ARCHIVES OF SURGERY

VOLUME 41 OCTOBER 1940 NUMBER 4

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EXPERIMENTAL STUDIES ON HEADACHE

PAIN-SENSITIVE STRUCTURES OF THE HEAD AND THEIR SIGNIFICANCE IN HEADACHE

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Studies on man and lower animals have shown that the cranial blood vessels are pain-sensitive structures, capable under special circumstances of giving rise to headache.[1] The distention of cerebral arteries is primarily responsible for the headache produced by certain chemical agents, of which histamine is representative;[2] the headache associated with septicemia and fever is in the same category.[3] It has been shown that the afferent fibers from the pain-sensitive cerebral arteries above the tentorium enter the brain stem primarily through the fifth cranial nerve, whereas the fibers from the arteries below the tentorium enter the nervous system chiefly through the upper cervical nerves.[4] The disten-

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tion of certain branches of the external carotid arteries is chiefly responsible for migraine headache and the headache associated with arterial hypertension.[5]

Thus, data about the great variety of headaches resulting from distention of cranial arteries are specific, but there is lacking detailed information about the sensitivity to pain of the majority of the structures of the head, essential to an understanding of other varieties of headache. Moreover, little precise information exists concerning either the sites of reference when pain-sensitive structures are stimulated or of the pathways that convey the impulses interpreted as headache. The demonstration at postmortem examination and by histologic methods of the presence of nerve fibers or nerve endings in a given structure does not in itself justify the inference that the structure is sensitive to pain; afferent fibers cannot be distinguished with certainty from efferent, nor can pain-conducting afferent fibers and end organs be differentiated from other afferent nerves. It is desirable, therefore, to turn to a more direct method of study, and to this end an excellent opportunity is offered during surgical procedures on the head.

Surgeons who employ local anesthesia during surgical procedures on the brain are aware that some intracranial structures are more sensitive than others. However, impressions with regard to sensitivity may be inexact unless special care is taken to make accurate and repeated determinations and recordings. Valuable observations concerning sensitivity to pain have already been made.[6]

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During the last five years an attempt has been made in this clinic to acquire in an orderly way from patients during operative procedures a more exact knowledge of the sensitivity to pain of structures inside and outside the cranium. It is the purpose of this communication to present the data thus acquired and to consider their clinical significance.

METHOD

As a basis for this study, there was selected from a large group a limited series of 30 patients.[7] The following conditions were required:

1. Surgical exposure of the lesions of the brain afforded an opportunity to make careful observations on the sensitivity to pain of the structures within and outside the cranium.

2. The patients were intelligent and cooperative, so that not only could pain be reported but its site and nature could be described.

3. The patients were relatively free of apprehension and of preoccupation with pain, so that a minimal amount of local and general analgesia was required.

4. The operative procedures were such that the patients were not too prostrated or inarticulate to describe their sensations.

5. The structures in every case were free of any disease process. This was necessary to insure normal responses to stimulation.

6. The observations were recorded in detail and by appropriate charts at the time they were being made in the operating room. The records included the site and kind of stimulation and the localization and nature of the pain when it resulted.

The type of stimulation employed in each instance will be included in the data on the following structures.

OBSERVATIONS

Scalp, Galea, Fascia and Muscle.—One hundred and fifty observations were made on 30 subjects.

The scalp was sensitive to all the usual forms of thermal, chemical, mechanical and electrical stimulation. The galea was sensitive to pain but otherwise insensitive. Where the blood vessels were in close contact

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New Points in Its Anatomy, Physiology and Pathology, J. Neuropath. & Psychopath. **17**:193, 1937. (*l*) Northfield, D. W. C.: Some Observations on Headache (Hunterian Lecture, Abridged), Brain **61**:133, 1938. (*m*) Penfield, W., and McNaughton, F.: Dural Headache and the Innervation of the Dura Mater, Tr. Am. Neurol. A. **64**:106, 1938. (*n*) McNaughton, F.: The Innervation of the Intracranial Blood Vessels and Dural Sinuses, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:178, 1938. (*o*) Fay, T.: Problems of Pain Reference to the Extremities, Am. J. Surg. **44**:52, 1939.

7. Observations on 15 additional cases have verified the foregoing data.

with the galea there was usually greater sensitivity to pain than at other places. The fascia covering the temporal and occipital muscles and also the muscles themselves were everywhere sensitive to pain. The pain arising in all these structures usually was experienced somewhere near the region of the stimulus.

Periosteum of the Skull (Epicranium).—One hundred observations were made on 30 subjects.

The periosteum had a variable sensitivity to pain. On the whole it was not particularly sensitive, and in spots over the vertex it was entirely insensitive. In general, the sensitivity increased in the regions just over the brow, low in the temporal regions and low in the occipital regions. Always when a periosteal elevator was used to strip up the periosteum around the base of the skull there was a complaint of moderate pain, felt somewhere in the neighborhood of the point of stimulation.

Cranial Bone, Including Diploic and Emissary Veins.—The cranial bone was everywhere insensitive. This was demonstrated many times in the process of drilling, sawing, rongeuring and coagulating at all points of the skull. This general statement is valid for the inner and outer tables and the cancellous central portion. It may further be stated that when there was occasion to test for pain in regions of endostoses and exostoses, which were sometimes highly vascularized, there was still no evidence of sensation (3 subjects, 12 observations). The venous channels (diploic veins) of the bone were also insensitive on faradic stimulation (3 subjects, 12 observations). There was occasion to stimulate directly the walls of some of the larger diploic veins both with faradic current and by the coagulating endothermy; no pain was elicited. Specifically, the principal diploic veins studied were the occipital, the mastoid and the large lateral venous channels. The walls of the occipital and mastoid emissary veins just outside the skull (fig. 1 *A*) were directly stimulated with faradic current and found to be insensitive (3 subjects, 12 observations [fig. 1 *A*]).

Extracranial Arteries and Veins.—All of the arteries of the scalp were found to be sensitive to pain, whereas the veins were much less so or not at all (fig. 1 *B*). The principal extracranial artery is the superficial temporal, which is a branch of the external carotid artery and supplies the larger portion of the parietal region. The supraorbital and the frontal arteries are branches of the ophthalmic artery (itself a branch of the internal carotid artery) and supply the frontal region. The occipital arteries and the postauricular arteries are branches of the external carotid artery and supply the occipital and suboccipital regions. There are veins corresponding to each of these main arteries. By various methods it was demonstrated that the main trunks of all of these arteries

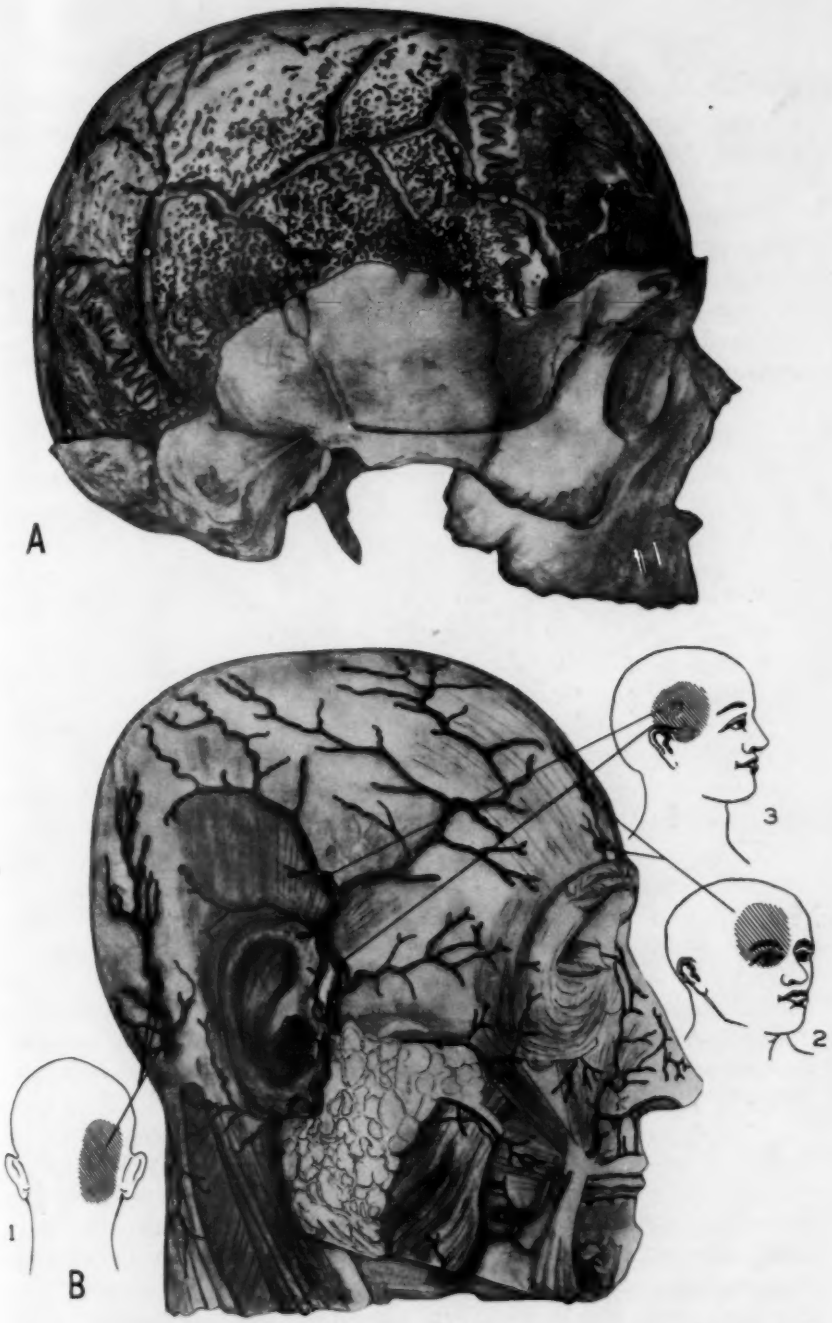

Fig. 1.—*A*, view of the diploic and emissary veins of the cranium. ○ indicates the point of stimulation without pain. *B*, view of the arteries of the scalp. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of (*1*) the occipital arteries; (*2*) the supraorbital and frontal arteries, and (*3*) the superficial temporal artery.

were sensitive to pain. The stimuli employed included faradic current, burning, distending, stretching and crushing (temporal artery, 6 subjects, with 24 observations; occipital artery, 5 subjects, with 20 observations; frontal and supraorbital arteries, 2 subjects, with 8 observations).

Stimulation of two different points 3 cm. or more apart caused pain which was localized at slightly different sites. Charts of the observations showed that in each instance the pain was felt in the general region of the point of stimulation and that stimulation of both points at once produced pain over a larger area than a combination of the two painful areas produced previously (fig. 2).

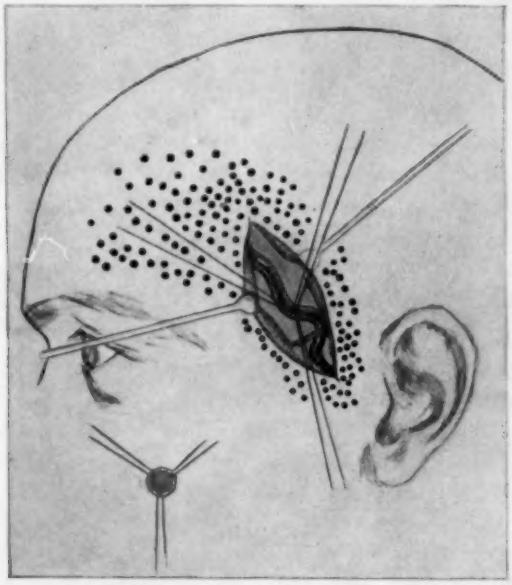

Fig. 2.—View of traction sutures symmetrically placed in the wall of the superficial temporal artery. The mechanical distention of the artery resulting from simultaneous traction on all three sutures caused pain in the dotted area.

Distention of an artery by stretching its walls with the spread of a clamp inside its lumen elicited pain, and an intermittent pain followed alternate spreading and closing of the clamp. Distention was effected in still another way, by means of three fine silk threads attached to the wall of the temporal artery and so spaced in relation to each other that when they were pulled simultaneously the temporal artery was distended without interference with the blood flow. Passing the fine curved needles through the outer layers of the arterial wall produced no sensation. Gentle pressure likewise was not perceived, although pinching was associated with pain. It was observed that distention induced in the manner indicated, that is, by pulling the three threads simultaneously, produced a

well localized pain in the temporal region, in an area about 5 cm. in diameter. The pain was aching, persisted as long as distention was maintained and promptly ceased when it was discontinued. By repeatedly and rhythmically distending and collapsing the artery a throbbing quality could be given to the headache. When the threads were applied in the aforementioned manner in two places, one nearer the ear and one about 1.5 cm. farther toward the temporal region, distention by pulling on either group of threads produced pain similar to that just described, but the areas of discomfort were separately located, the one nearer the ear and the other over the temple. When the two groups were pulled simultaneously, so that distention occurred at two separate sites, the ache seemed to be more widespread than the sum of the two painful areas produced previously, and the headache then seemed to reach from the front of the ear to the middle of the supraorbital ridge. The headache resulting from this distention was associated with a feeling of nausea or sickness. Longitudinal stretch of an artery was painful in the same manner as the lateral stretch of distention.

Constriction of the lumen was not painful. The repeated application of epinephrine to exposed and otherwise pain-sensitive arteries caused vigorous constriction of the vessels but no pain. Crushing and stroking of the arterial wall always resulted in pain.

In all such experiments no procaine hydrochloride was employed in the region about the artery. The introduction of procaine hydrochloride into the adventitia of the temporal artery immediately produced anesthesia to all stimuli a few centimeters distal to the point of injection. The implication is that the sensory nerve supply originates near and travels along with the arteries. It should be pointed out that sometimes a number of small visible nerves were seen passing along the course of these arteries, and this was particularly true of the supraorbital and occipital arteries. To be sure, direct stimulation of these nerves was painful, but the tests referred to were all on the artery itself after it had been separated from any visible adjacent nerve trunk. Since the temporal artery has a rich anastomosis with the supraorbital and frontal arteries anteriorly and the occipital arteries posteriorly, there is reason to assume that there is also a free overlapping of the nerves supplying these vessels. Hence, even when the nerve supply of the temporal artery was blocked in the temporal region, if one of the main branches of this artery was traced far enough anteriorly or posteriorly it was again found to be sensitive, presumably because of an additional nerve supply from these areas.

The anterior and posterior arteries of the scalp, that is, the frontal, supraorbital, postauricular and occipital arteries, were found to be sensitive to crushing, burning and stretching, just as were the temporal arteries.

Dural Arteries.—The principal dural artery is the middle meningeal, a branch of the external carotid artery which supplies all of the supratentorial dura except for the dura of the floor of the anterior fossa and that over the anterior pole of the brain. The latter dura is supplied by the anterior meningeal arteries and by branches of the internal carotid and of the ethmoidal arteries. The subtentorial dura is supplied by the posterior meningeal arteries, branches of the occipital, vertebral or ascending pharyngeal arteries.

As in the observations on the arteries of the scalp, it was demonstrated that the main trunks of all the dural arteries were sensitive to painful stimuli. The stimuli employed included faradizing, burning, distending, stroking, stretching and crushing (middle meningeal artery and its branches, 11 subjects and 96 observations [fig. 3 *A*]). Distention was effected just as it was in testing the sensitivity to pain of the superficial temporal artery; on one occasion the tip of a clamp was introduced into the lumen of the middle meningeal artery and spread, and on another a series of silk sutures equally placed about the circumference of the artery were simultaneously pulled on (fig. 3 *B*). The pain produced was localized fairly accurately in the area of distention and also was commonly described as being in the back of the eye. It was aching, similar to that resulting from distention of the temporal artery. It also was accompanied by nausea.

A few of the smaller branches arising from the main divisions of the middle meningeal artery, even within a few centimeters of the midline at the vertex, were found to be sensitive to pain. The area in which the pain was felt was usually fairly discrete and was somewhere in the region of stimulation. In general, the pain experienced from stimulation of the middle meningeal artery was within the homolateral temporoparietal region and was deep and aching. It could be shown that there was a slight discrepancy in the exact localization when different parts of the artery were stimulated. Thus, pain arising from the main trunk of the artery and the more proximal part of the anterior branch was felt in the midtemporal region; pain arising from the more distal divisions of the anterior branch was more parietal in its location, and pain arising from the posterior branches of the artery was localized behind both of the other two sites.

The usual experience associated with reflection of a temporoparietal osteoplastic flap was the occurrence of sharp pain in that general region as a result of stretching the middle meningeal artery or tearing it from its groove in the bone (24 subjects, 24 observations). The severity of the pain was variable but usually comparable to that from painful superficial structures and more severe than that arising from stimulation of most pain-sensitive intracranial structures. This impression was substantiated by application of other stimuli to the artery. Although distention of a

main trunk of the artery by some mechanical means repeatedly caused pain, vigorous constriction of the arterial wall after local application of epinephrine was unaccompanied by pain. These findings conformed to those made on similarly testing the superficial temporal artery.

Transection, ligation or procaine hydrochloride infiltration of the midmeningeal artery anywhere along its course, even as far proximal as the foramen spinosum, was always followed by anesthesia of the artery distal to that point. This finding plus the further observation that the dura which lies between the branches of the midmeningeal artery was insensitive to pain indicates that the pain-conducting fibers join the artery near its origin and travel adjacent to it.

The localization of pain from stimulation of the anterior meningeal arteries was limited to the forehead and the region of the eye on the same side (12 subjects, 48 observations). That from the posterior meningeal arteries was limited to the back of the head on the same side (4 subjects, 16 observations). The sensitivity to pain of the anterior and posterior meningeal arteries was limited to the most proximal portions of these quickly arborizing vessels, and the small distal branches in the dura over the frontal poles of the cerebrum and over the cerebellar lobes were insensitive to pain.

Dura, Supratentorial.—The supratentorial dura (fig. 4) covering the convexities of the cerebrum and exclusive of the base was found to be entirely insensitive to all forms of stimulation except along the margins of the dural sinuses and along the course of the middle meningeal artery (11 subjects, 148 observations).

The entire dural floor of the anterior fossa (12 subjects, 48 observations), on the contrary, while inconstantly sensitive to pressure, was almost uniformly sensitive to faradic stimulation, and the pain arising from this region was localized to the homolateral eye, that is, over, within, behind or beside the eye. Sometimes, stimulation of the floor of the anterior fossa at widely separated points caused pain at slightly different sites within the general region about the eye. The dura of the olfactory groove was found to be unusually sensitive to pain, while the dura that forms the roof of the orbit was perhaps slightly less so. The dura along the superior aspect of the sphenoidal ridge, in the region of the dorsum sellae and at the base of the anterior clinoids was but moderately sensitive. At the lateral and anterior margins of the floor of the fossa, that is, lateral and anterior to the roof of the orbit, the dura became progressively less sensitive to pain and was finally insensitive at points 2 cm. or more above the floor (fig. 5).

As an example of the occasional variation from the normal in the presence of a local disease process, the following experience deserves mention. The dura several centimeters above the floor of the anterior fossa was found to be sensitive in the presence of a large meningioma of this region which had a wide attachment to the dura of the floor of

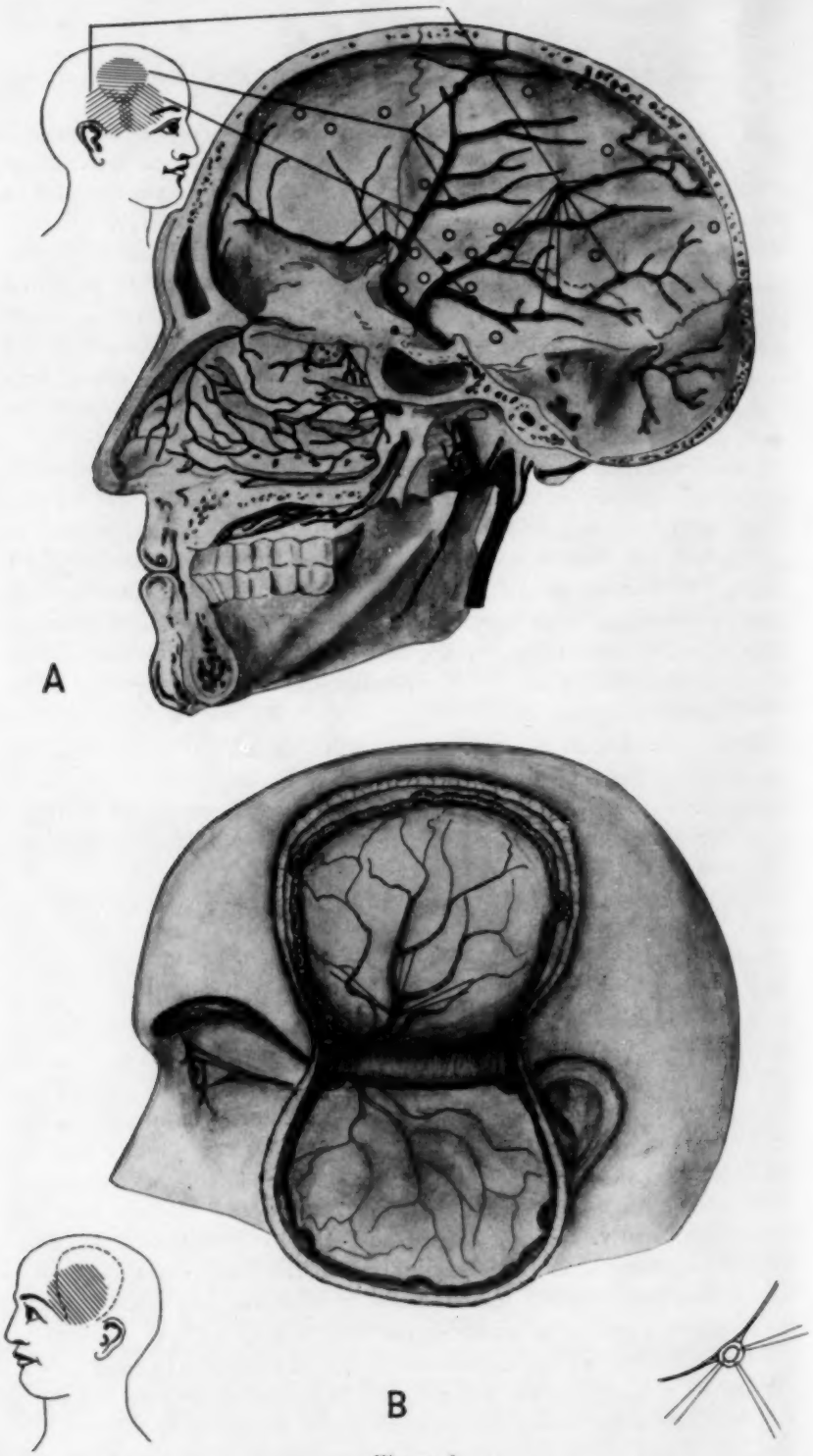

Figure 3

(See legend on opposite page)

this fossa and above. Furthermore, arteries over the convexity and within the substance of the tumor which had doubtless grown in from the anterior meningeal arteries were sensitive to pain. The pain arising from stimulation of these arteries and from the dura about the upper margins of the tumor's attachment was experienced in the region about the eye, just as was noted after stimulation of the normal dura and dural arteries on the floor of the anterior fossa.

It should be emphasized that, while visible portions of the dural arteries of the floor of the anterior fossa were sensitive to pain, the dura which lies between these vessels was itself sensitive to pain. The tests were made when the tissue was dry, so that spread of the stimulation was minimal. A similar arrangement was found to exist in the posterior fossa. But the same was not true for any part of the floor of the middle fossa. Here the dura was insensitive. While all the principal branches of the middle meningeal artery were sensitive to pain, the dura at all points more than 2 mm. away from such vessels was insensitive to all the aforementioned forms of stimulation. The floor of the middle fossa (fig. 5) was examined as far medially as the foramen lacerum and the cavernous sinus (4 subjects, 20 observations).

Stimulation of the dural capsule of the components of the fifth cranial nerve resulted in pain usually distributed over the face, and it was impossible to determine whether the nerve itself rather than its capsule was receiving the stimulus. Suffice it to say that whatever served to stimulate the capsule doubtless stimulated the nerve also.

Dura of the Sella Turcica and Diaphragma Sellae.—There was opportunity to make observations on the dura and diaphragma of the sella only when tumors existed in the region, and in these instances the dura was more or less attenuated from distortion and compression by the tumor. Faradic stimulation of the thinned-out diaphragma in a case of pituitary adenoma failed to cause pain. Pressure on this structure and also tearing it by spreading its fibers with a clamp produced pain experienced just behind the eye, yet crushing the torn edge did not cause pain. It appeared that the pain induced by pressure and tearing was the result of distortion of the pain-sensitive carotid artery nearby (3 subjects, 20 observations).

EXPLANATION OF FIGURE 3

Fig. 3.—*A*, view of the middle meningeal artery. ○ indicates the point of stimulation of the dura without pain. ● indicates the point of stimulation causing pain. The diagram shows three overlapping areas of pain in the parietotemporal region resulting from stimulation of different portions of the artery and its branches. *B*, view of traction sutures symmetrically placed in the wall of the middle meningeal artery. The mechanical distention of the artery resulting from simultaneous traction on all three sutures caused pain in the hatched area on the diagram.

The only opportunity for studying the dura lining the sella occurred on the occasion of introduction of a suction tube into the depths of the sella or pulling with forceps on the deep fragments of a pituitary adenoma. Both of these methods of stimulation in 1 subject produced pain near the top of the head. Furthermore, if the stimulus was applied to the left side of the sella the pain was felt to the left of the midline at the vertex; the opposite was true for the other side. In this case it was known that the roof of the sphenoid sinus had collapsed, and it is possible that the membranous lining of the sinus was being stimulated and was the cause of the pain at the vertex.

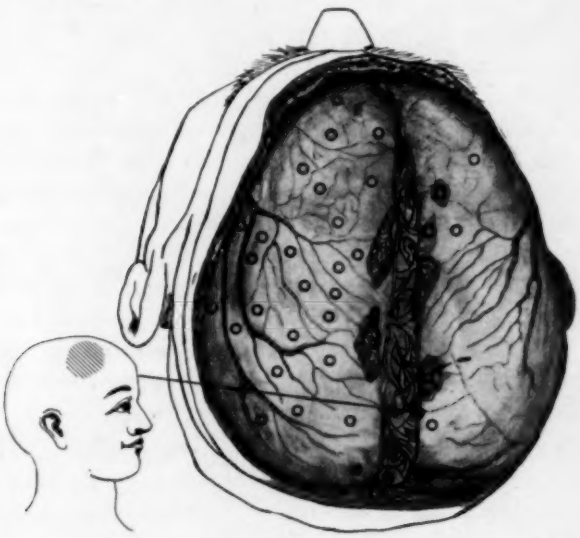

Fig. 4.—View of the superior sagittal sinus and the adjacent venous lacunae and arachnoid granulations. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagram shows the area of pain following stimulation of the margin of the superior sagittal sinus.

Dura of the Posterior Fossa.—The dura over the convexity of the cerebellar hemispheres was everywhere insensitive to pain except along the margins of the occipital and transverse sinuses (6 subjects, 150 observations). The floor of the posterior fossa, on the other hand, was uniformly sensitive in a fashion comparable to that of the anterior fossa. Roughly, the floor of the posterior fossa was taken to be that more or less triangular region which lies between the rim of the foramen magnum and the lateral attachment of the tentorium cerebelli. Observations with closely spaced stimulation of the dura of this region revealed that, while the entire area was sensitive to pain, from some points the pain was felt just behind the homolateral ear, and from other points it was felt in the back of the head.

That portion of the dura which lay over or was near the margins of the lateral (sigmoid) sinus when stimulated caused pain behind the ear (2 subjects, 8 observations). Section of the ninth and tenth

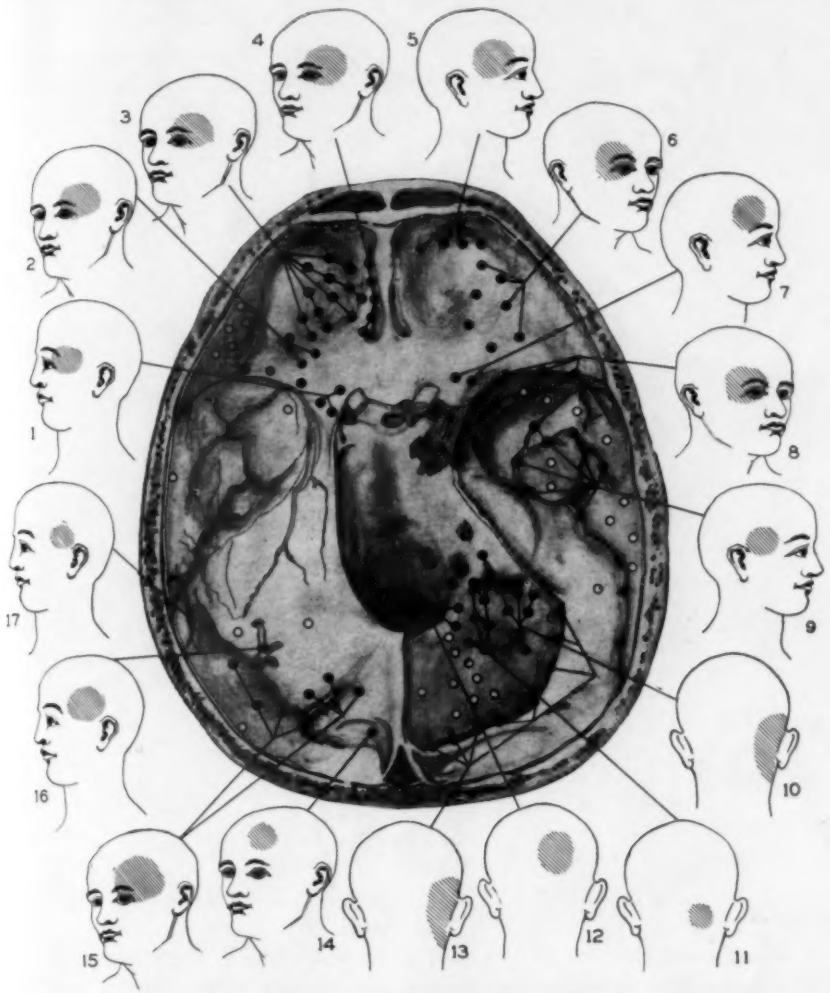

Fig. 5.—View of the dural floor of the skull, the tentorium cerebelli and the adjacent venous sinuses and venous tributaries. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of (*1* to *8*) the dura of the floor of the anterior fossa; (*9* and *17*) the middle meningeal artery; (*10* to *12*) the dura of the floor of the posterior fossa; (*13*) the inferior wall of the transverse sinus; (*14*) the superior wall of the torcular Herophili; (*15*) the superior wall of the transverse sinus and upper surface of the tentorium cerebelli, and (*16*) the inferior cerebral veins.

cranial nerves in 1 of the patients made it impossible to elicit pain on subsequent stimulation of the aforementioned dural and sinal structures. Stimulation of the remaining and more mesial portion of the dura, extending to the rim of the foramen magnum, caused pain low in the

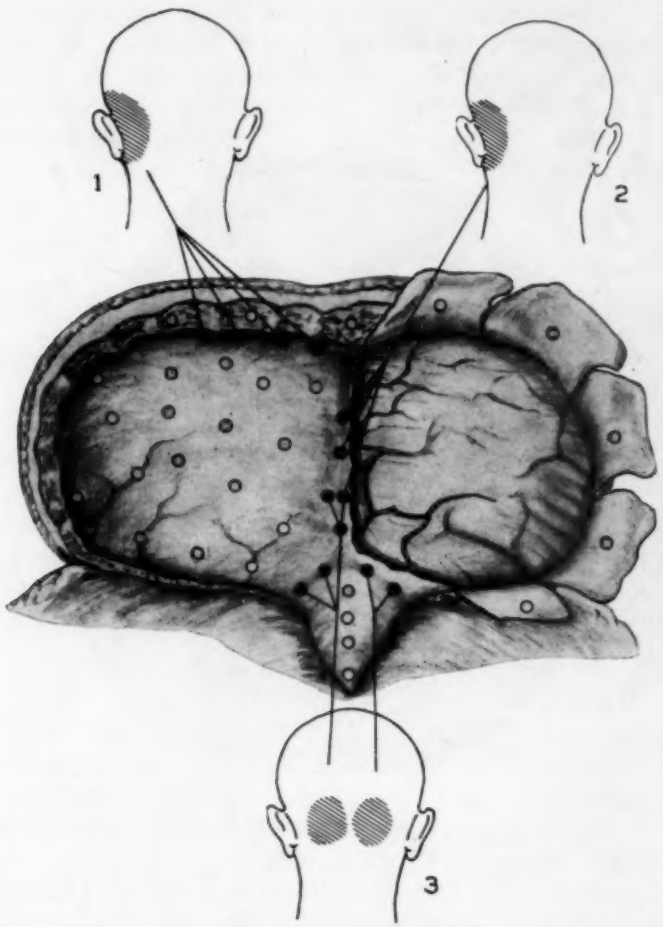

Fig. 6.—View of the venous sinuses and the dura over the cerebellum and the upper part of the cord. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of: (*1*) the transverse sinus; (*2*) the torcular Herophili and upper part of the occipital sinus, and (*3*) the lower part of the occipital sinus.

back of the head (2 subjects, 14 observations). This region of the dura was sometimes seen to be traversed by small branches of the posterior

meningeal arteries, and the localization of the pain following stimulation was the same for both the dura and the arteries (2 subjects, 8 observations). Section of the posterior roots of the first three cervical nerves in one of the patients made it impossible to elicit pain on subsequent stimulation of the aforementioned dural and arterial structures. There was no occasion to visualize or stimulate the dura which lies beneath the brain stem and covers the clivus blumenbachii (figs. 5, 7 and 8).

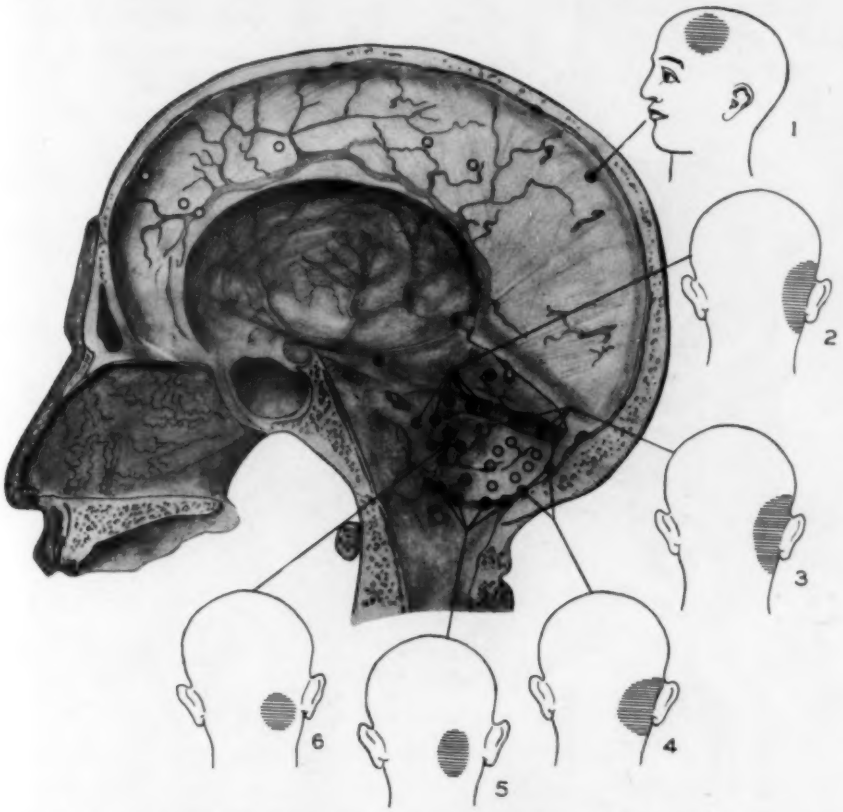

Fig. 7.—View of the falx cerebri, the dura and venous sinuses of the posterior fossa. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of: (*1*) the superior sagittal sinus; (*2*) the sigmoid sinus; (*3*) the transverse sinus; (*4*) the upper part of the occipital sinus; (*5*) the lower part of the occipital sinus, and (*6*) the dura of the floor of the posterior fossa.

Falx.—It was found that burning, cutting, faradic stimulation and pressure along the anteroposterior extent of the falx failed to produce pain unless the margins of the superior sagittal sinus were displaced or

encroached on (5 subjects, 35 observations). An exception to this general finding on the sensitivity of the falx was the observation that faradic stimulation of the first few centimeters above its attachment to the crista galli caused pain in and about the homolateral eye (2 subjects, 6 observations). There was opportunity to explore the inferior margin of the falx only along the anterior half of its border with the inferior

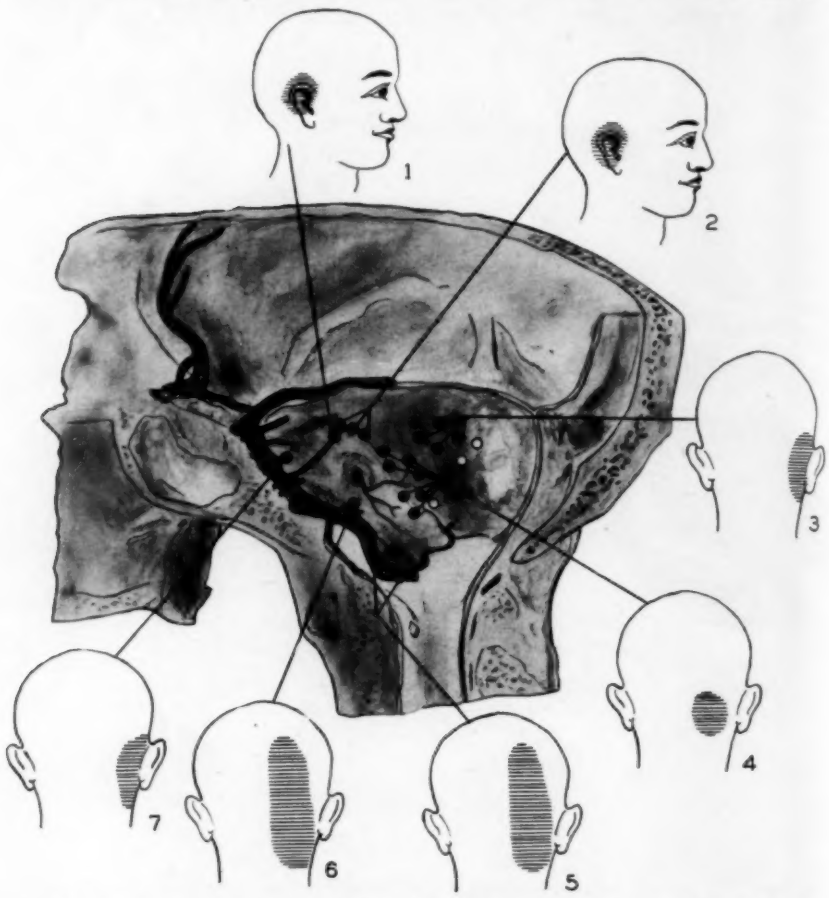

Fig. 8.—View of the arteries and dura of the posterior fossa. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of: (*1*) the internal auditory artery; (*2*) the dura at the porus acusticus; (*3*) the wall of the sigmoid sinus and the adjacent dura; (*4*) the dura near the rim of the foramen magnum; (*5*) the vertebral artery; (*6*) the posterior inferior cerebellar artery, and (*7*) a pontile artery.

sagittal sinus; this much of it was found to be insensitive. Lateral pressure against the falx with a blunt ventricular needle was exerted to a

degree sufficient almost to puncture this tough structure, without causing pain. Sometimes the point of pressure was within 2 cm. of the superior sagittal sinus, yet pain did not result (figs. 7 and 9).

Tentorium Cerebelli.—On the superior surface of the tentorium it was found that pressure against its central portion caused pain in the homolateral side of the forehead and the region of the homolateral eye. Faradic stimulation of this surface in spotty areas of apparently fortuitous distribution (fig. 5) caused pain in the same region (4 subjects, 20 observations).

On the inferior surface of the tentorium the findings at first appeared variable but eventually permitted inferences to be drawn. Slight or even

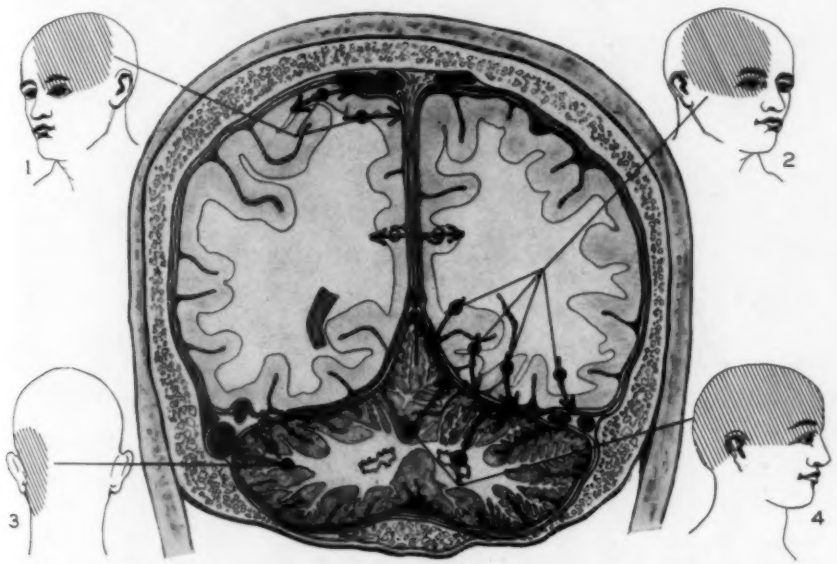

Fig. 9.—View of a coronal section through the head, showing the falx cerebri, the tentorium cerebelli and the associated venous sinuses. ⌀ indicates the point of stimulation of the falx cerebri without pain. ● indicates the point of stimulation causing pain. ◎ indicates the point at which stimulation of greater intensity than usual is required to produce pain. The diagrams show the area of pain following stimulation of: (*1*) the superior sagittal sinus and tributary veins; (*2*) the superior surface of the tentorium cerebelli and wall of the transverse sinus; (*3*) the inferior wall of the transverse sinus, and (*4*) the inferior surface of the tentorium cerebelli, resulting in secondary effects on *2* and *3*.

moderate pressure upward usually failed to cause pain unless the margins of the venous sinuses were approached, in which case pain was usually experienced behind the homolateral ear. When pressure on the center of the tentorium was increased, pain occurred behind the ear, in the region of the forehead and eye on that side or in both regions. Strong

pressure applied at a point near the free edge at the side of the pons in 1 case caused pain low in the back of the head on the same side, apparently because of secondary displacement of some other pain-sensitive structure. Faradic stimulation of sufficient intensity to induce pain in the structures with well established sensitivity to pain (figs. 9 and 10) failed to cause pain when applied to points on the undersurface of the tentorium more

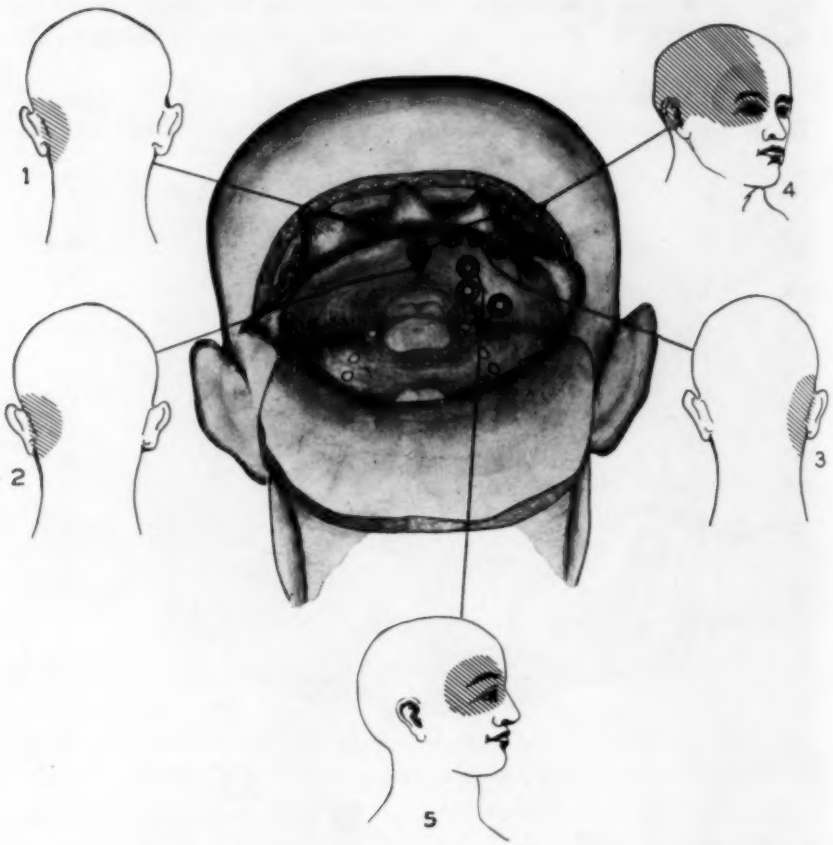

Fig. 10.—View of the undersurface of the tentorium cerebelli. ● indicates the point at which stimuli of usual intensity cause pain; the diagrams show the area of pain following stimulation of: (*1*) the torcular Herophili; (*2*) the straight sinus, and (*3*) the transverse sinus. ◎ indicates the point at which stimuli of usual intensity cause no pain whereas stimuli of increased intensity cause frontal pain; diagram *5* shows the area of pain following stimulation of the undersurface of the tentorium cerebelli. ◉ indicates the point at which stimuli of usual intensity cause pain behind the homolateral ear whereas stimuli of increased intensity cause pain over the entire homolateral side of the head; diagram *4* shows the area of pain following stimulation of the transverse and straight sinuses.

than 5 mm. from the venous sinuses. It was found further, however, that if the intensity of the stimulus was increased sufficiently pain was experienced in the forehead and in the region of the eye on that side, suggesting that the stimulus was transmitted through the tentorium to its superior surface (5 subjects, 35 observations).

Dural Sinuses and Their Tributary Veins.—Superior Sagittal Sinus: The walls of the major extent of this sinus were found to be sensitive to pain, although in general the pain produced was only moderately intense

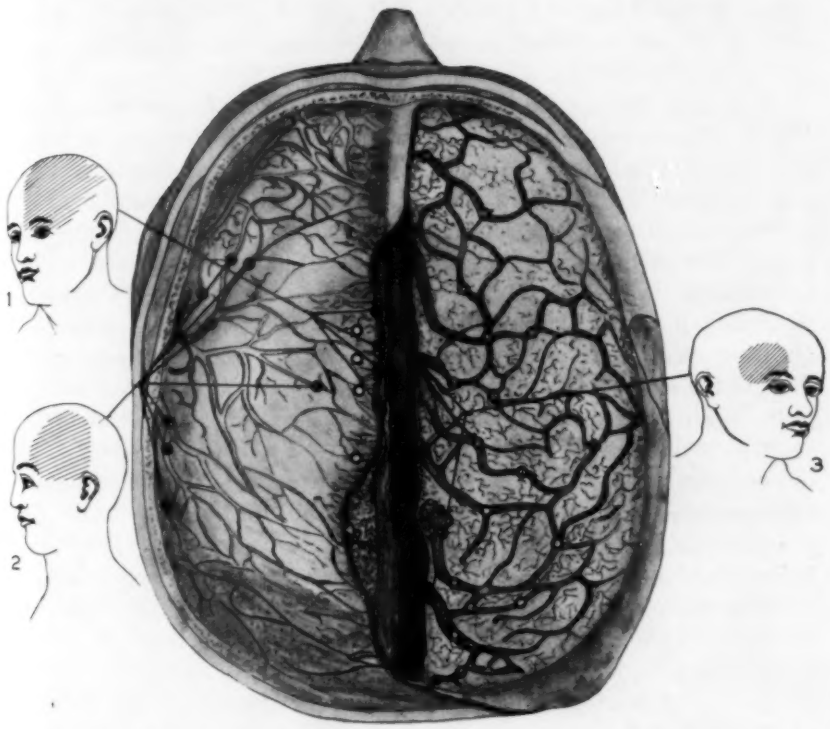

Fig. 11.—View with the calvarium removed. The dura and the meningeal arteries are shown on the left; the cerebral and tributary veins are shown on the right. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of: (*1*) the margin of the superior sagittal sinus; (*2*) the middle meningeal artery, and (*3*) the tributary veins to the superior sagittal sinus.

as compared with that resulting from stimulation of the middle meningeal artery or of the large arteries at the base of the brain. Pressure, traction and faradic stimulation were used. In addition, it was discovered that stripping the dural wall away from its attachments to the cranial vault produced slight pain. In its more anterior portion, that is, along

its first 7 or 8 cm., the sinus was either insensitive or much less sensitive than in its middle and posterior thirds. Pain in the frontal part of the head and in the region of the eye usually followed stimulation of the sensitive regions. Sometimes the pain arising from the more anterior half of the sinus was localized in the parietal region, near the vertex. It was also noted, although it was impossible to define the area accurately, that the middle third of the sinus lost some of its sensitivity after an incision through the dura that traversed the main trunk of the middle meningeal artery and the nerves traveling along with the artery. The side of the head on which pain was felt (figs. 4 and 11) was always the same as the side on which the wall of the sinus was stimulated (8 subjects, 32 observations).

Tributary Veins to the Superior Sagittal Sinus (Superior Cerebral Veins): These veins, which pass from the cerebral cortex to the sinus, were found to be insensitive to coagulation, crushing and faradic stimulation except for the few millimeters of vessel next to the sinus. However, traction on the vessels at all points along the extent of the sinus produced pain in the same sites as that caused by direct stimulation of the adjacent wall of the sinus (8 subjects, 32 observations). There was variability in the occurrence and degree of the pain resulting from traction on these veins, but sometimes, and particularly along the posterior third of the sagittal sinus, very slight traction caused moderately intense pain. With the sudden collapse of a dilated lateral ventricle, all of the veins passing from the cortex to the sagittal sinus were observed to be put on stretch, and at the same time there was pain in the homolateral frontoparietal and ocular regions (figs. 4, 9 and 11).

Pacchionian Granulations and Venous Lacunae: Pacchionian granulations were stimulated with faradic current without producing pain (3 subjects, 12 observations). It seemed likely that all such arachnoid extensions were insensitive. The walls of the venous lacunae at various points along the lateral margins of the sagittal sinus (fig. 4) also were insensitive to burning, pressure and faradic stimulation (3 subjects, 12 observations).

Inferior Sagittal Sinus: The inferior sagittal sinus was stimulated only along its anterior 5 to 6 cm., and in this region the channel is of smaller caliber and has few or no tributaries from the cerebrum (fig. 7). When this anterior portion of the sinus was crushed or stimulated with faradic current it was found to be insensitive (4 subjects, 12 observations).

Transverse Sinus, Torcular Herophili and Straight Sinus (Supratentorial Surfaces): Stimulation of the walls of the transverse sinuses and torcular Herophili on their supratentorial surfaces by faradic current uniformly caused pain in the region of the homolateral side of the forehead and the homolateral eye (4 subjects, 16 observations). The stimulation that resulted from pressure and gentle friction in the same

regions was insufficient to cause pain. Only a short segment of the straight sinus near the torcular was available for study (3 subjects, 6 observations). Pain resulting from stimulation was felt in the homolateral side of the forehead and the homolateral eye. It was not possible to stimulate that part near the free edge of the tentorium, nor were the veins of Galen investigated (figs. 5 and 9).

Inferior Cerebral Veins: The veins on the inferior surface of the temporal lobe were not sensitive to pain. But the main veins which pass from the undersurface of the temporal lobe to the lateral end of the transverse sinus and to the superior petrosal sinus were found invariably to be sensitive to crushing, burning, stretching and faradic stimulation. These veins, several in number and sometimes referred to as the veins of Labbé, were as long as 1.5 to 3 cm. in their extracerebral course (figs. 5 and 12 *A*). When they were stimulated, the pain was experienced in the homolateral temporal region (3 subjects, 10 observations).

Occipital Sinus: That portion of the sinus that lies in the midline and extends from the torcular to the rim of the foramen magnum was uniformly sensitive to faradic stimulation, and the pain was experienced in one or both of two regions of the head (figs 6 and 7). Stimulation of the sinus near the torcular caused pain behind the ear, while stimulation near the foramen magnum caused pain low in the back of the head. After section of the posterior roots of the first three cervical nerves it was impossible to elicit pain on stimulation of the sinus near the foramen magnum. Just as was the case with the other midline sinuses, the superior sagittal and the straight, the side of the head on which pain was felt was homolateral to the side on which the wall of the sinus was stimulated. The divisions of this sinus which partly encircle the foramen magnum were also sensitive, and the pain was felt low in the back of the head (4 subjects, 20 observations).

Transverse Sinus, Torcular Herophili and Straight Sinus (Infratentorial Surfaces): Stimulation of the walls of these sinuses on their infratentorial surfaces by faradic current uniformly caused pain in an area behind the homolateral ear (6 subjects, 24 observations). In addition, it was found that if a current of greater intensity was employed pain was also felt in the homolateral side of the forehead and near the homolateral eye. The tributary veins from the cerebellum to these sinuses were found to lack sensitivity to pain when stimulated with faradic current, crushed or put on slight traction (figs. 6, 7 and 10).

The wall of the lateral portion of the transverse sinus (sigmoid sinus) was stimulated from the inside of the posterior fossa (figs. 5, 7 and 8). The margins of the sinus here are indistinct, but faradic stimulation of the dura overlying the sinus, from the margin of the tentorium to the jugular foramen, uniformly caused pain behind the homolateral ear (see section on the dura of the posterior fossa).

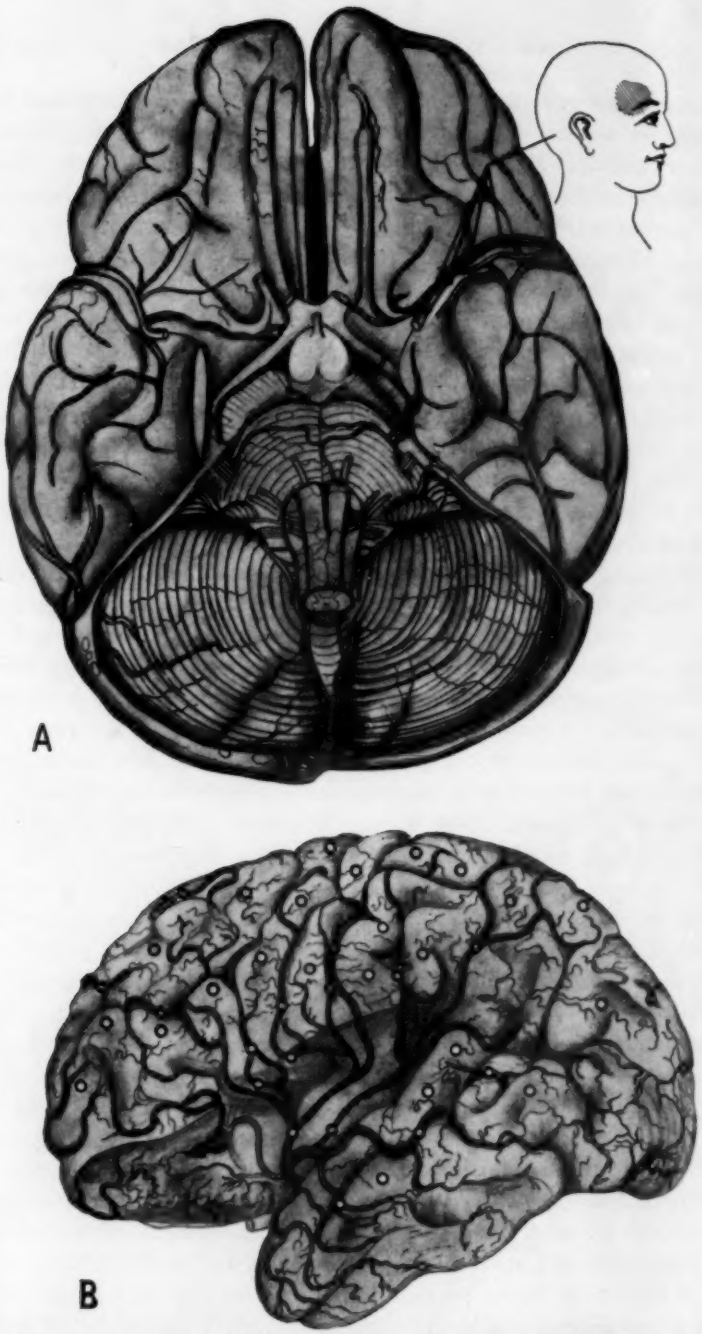

Fig. 12.—*A*, view of the veins at the base of the brain. ● indicates the point of stimulation causing pain. The diagram shows the area of pain following stimulation of the deep segment of the sylvian vein. *B*, view of the arteries over the cerebral cortex. ○ indicates the point of stimulation without pain.

The wall of the cavernous sinus in 1 subject was stimulated at the point where the midcerebral vein joined it. Faradic stimulation here caused pain in the homolateral ocular and maxillary region. Since the ophthalmic and maxillary nerves lie in the lateral wall of the sinus, it is probable that they were being stimulated directly.

There was no opportunity to stimulate directly the more inaccessible venous channels, which include the petrosal sinuses and the basilar plexus.

Pia-Arachnoid.—The pia-arachnoid covering the convexity of the cerebral and cerebellar hemispheres was found to be insensitive to crushing, burning, stretching and faradic stimulation, with the possible exception of the pia-arachnoid very near to the great arteries at the base of the brain (30 subjects, 120 observations). It was found that tearing the pia-arachnoid surrounding the carotid arteries and the anterior part of the circle of Willis caused subjects to complain of pain, but this might well have been the result of secondary pull on these sensitive arteries (figs. 12 *B* and 13 *A*). The arachnoid forming the roof of the cisterna magna was found to lack sensitivity to pain (4 subjects, 12 observations).

Arteries and Veins of the Brain.—The pial arteries and veins over the superior and lateral convexities of the cerebrum (24 subjects, 300 observations) and the cerebellum (16 subjects, 150 observations) were found to lack sensitivity to pain with all forms of stimulation (figs. 12 *B* and 13 *A*).

However, as will be described, when pain resulted from stimulation of certain cerebral and pial arteries at the base, it was deep, intense, dull and aching. It was diffuse, yet grossly localizable, and it became throbbing when the stimulus was repeated. The pain, when prolonged, was associated with a feeling of nausea. When different pain-sensitive arteries were stimulated, the quality and intensity of pain that ensued were approximately of the same order, but the sites varied, as will be described.

The intracranial segment of the internal carotid artery was consistently sensitive to stretching, stroking and faradic stimulation (3 subjects, 10 observations). The pain was felt behind the eye and low in the temporal region on the same side (fig. 13 *B*).

The middle cerebral artery was found to be similarly sensitive along its proximal 1 to 2 cm. (3 subjects, 10 observations). Distal to this region, where the artery lies hidden in the lateral cerebral fissure and where it courses over the parietal lobe, it was not sensitive (20 subjects, 60 observations). Pain arising from the proximal segment had the same distribution in and behind the eye as did that from the internal carotid artery.

The anterior cerebral artery was found to be sensitive to crushing, stretching, burning and faradic stimulation from its point of origin to a point 1 cm. beyond the genu of the corpus callosum, a segment several

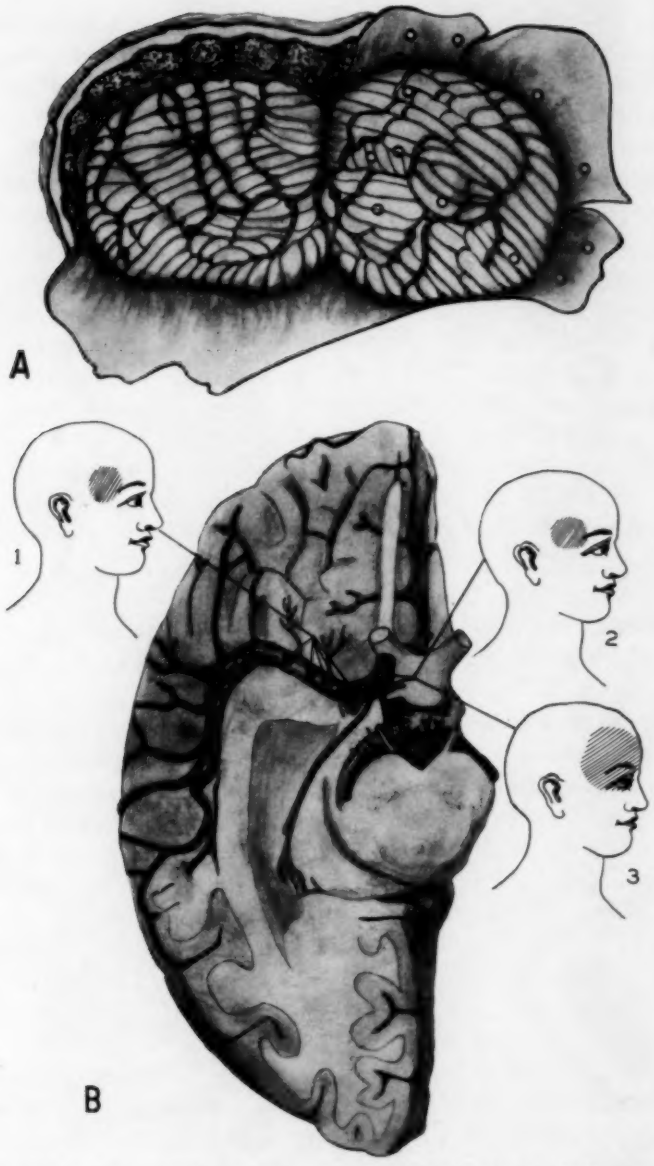

Fig. 13.—*A*, view of the arteries and veins over the cerebellar cortex. ○ indicates the point of stimulation without pain. *B*, view of the intracranial portion of the internal carotid artery and the proximal part of the middle cerebral artery. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of: (*1*) the middle cerebral artery and (*2* and *3*) the intracranial portion of the internal carotid artery.

centimeters in length (3 subjects, 12 observations). Beyond this point the artery was insensitive. The pain arising from the proximal segment was experienced in a rather poorly localized area behind and above the homolateral eye (fig. 14 *A*).

One of the principal pontile arteries at a point about 1.5 cm. from its origin (figs. 8 and 14 *B*) was found to be sensitive to pain on crushing, traction, coagulation and faradization, and the resulting pain was experienced behind the homolateral ear (1 subject, 4 observations).

The internal auditory artery, which accompanies the seventh and eighth cranial nerves (figs 8 and 14 *B*), was sensitive to stretching and faradic stimulation, and the pain was experienced in and just behind the homolateral ear (2 subjects, 8 observations).

The posterior-inferior cerebellar artery was sensitive to faradic stimulation and stretching in the proximal 1 to 2 cm. of its course (2 subjects, 8 observations); beyond this it was insensitive (6 subjects, 20 observations). The pain arising from the proximal segment was felt in a rather diffuse area in the homolateral occipital and suboccipital regions (figs. 8 and 14 *B*).

The vertebral artery, when stimulated by crushing, traction and faradic current, was sensitive to pain. The pain was slightly more intense but had the same distribution as that following stimulation of the posterior inferior cerebellar artery (figs. 8 and 14 *B*), that is, in the homolateral side of the occiput and suboccipit (1 subject, 5 observations).

Traction on numerous arteries at the base of the brain occurred when there was displacement of the brain stem by retraction during the removal of angle tumors. The pain associated with this maneuver was widespread but for the most part was experienced on the side of the head where vessels were being stretched. The pain associated with traction on the circle of Willis and its branches after distention of the third ventricle will be discussed later (see section on the third ventricle).

The middle cerebral vein, or sylvian vein, which runs in the lateral cerebral fissure to the cavernous sinus, was found on faradic stimulation to be uniformly sensitive to pain in the 3 to 4 cm. nearest the sinus but inconstantly sensitive higher. In 1 subject the vein was sensitive to pain well up on the lateral aspect of the brain. Retraction of the temporal lobe for the purpose of exposing the segment of the vein near the cavernous sinus did not put the vein on obvious traction, since it was rather closely adherent to the frontal lobe; the effect of traction on the vein was therefore not ascertained. The pain following stimulation of all sensitive points (fig. 12 *A*) was felt in the anterior temporal region and in the outer angle of the brow on the same side (4 subjects, 20 observations).

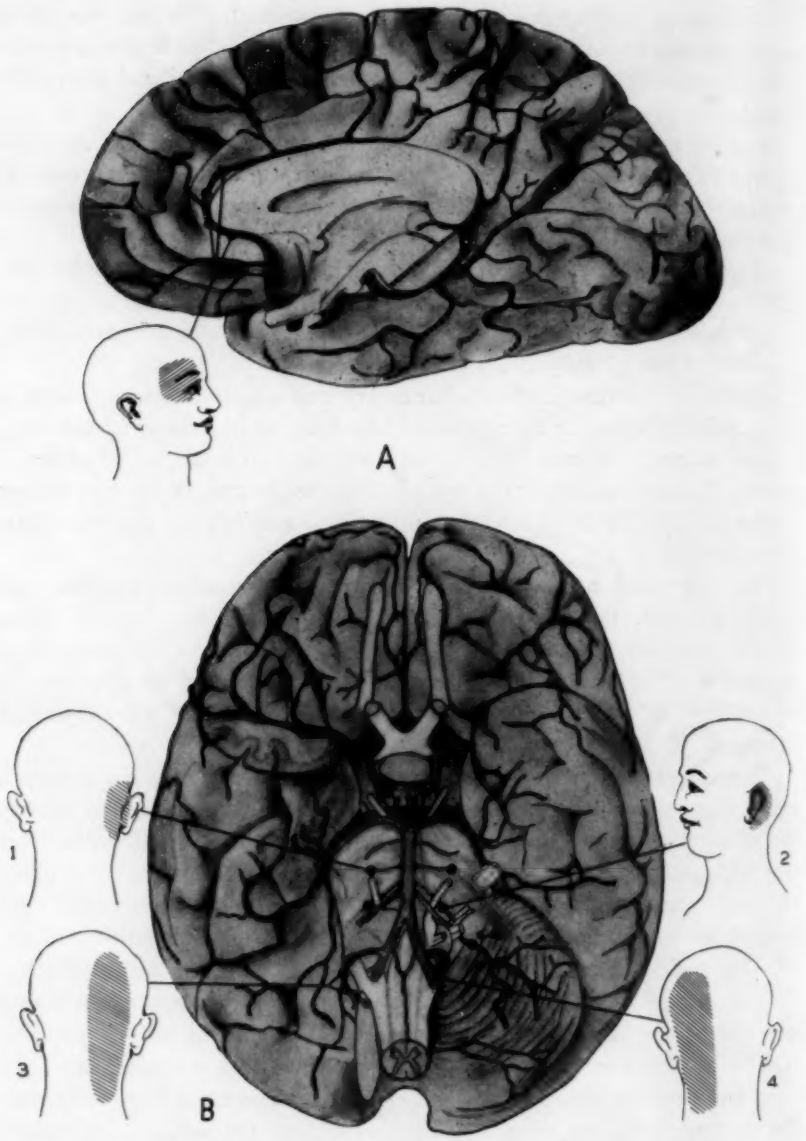

Fig. 14.—*A*, view of the anterior cerebral artery. ● indicates the point of stimulation causing pain. The diagram shows the area of pain following stimulation of the proximal segment of the artery. *B*, view of the arteries at the base of the brain. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of: (*1*) a pontile artery; (*2*) the internal auditory artery; (*3*) the proximal portion of the posterior inferior cerebellar artery, and (*4*) the vertebral artery.

Parenchyma and Nerves.—The entire parenchyma of the cerebrum and cerebellum, including the vessels found in it, was insensitive to all forms of stimulation (30 subjects). The olfactory, optic and auditory nerves were not sensitive to pain.

The cranial ninth and tenth nerves were each found, when stimulated, to cause pain behind the homolateral ear and in the throat. Stimulation of the eleventh cranial nerve caused pain low in the back of the head and in the upper cervical region on the same side. Stimulation of an inconstantly present posterior root of the first cervical nerve caused

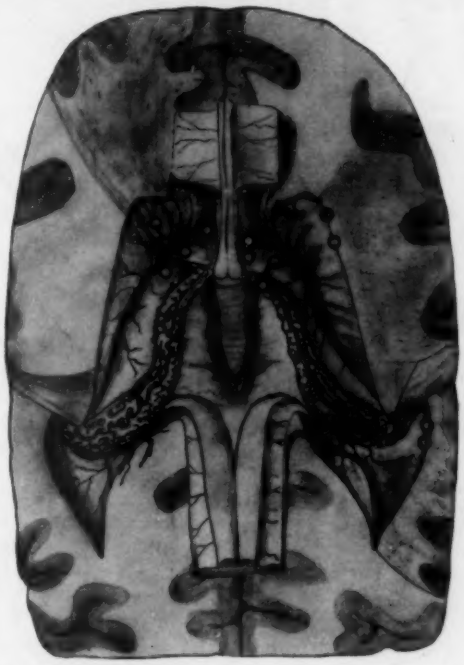

Fig. 15.—View of the lateral ventricles, the terminal veins, the choroid plexuses and the foramens of Monro. ◯ indicates the point of stimulation without pain.

pain near the vertex of the head, while stimulation of the second and third posterior roots caused pain at the vertex and back of the head and neck.

Ventricles, Aqueduct of Sylvius and Choroid Plexuses.—Lateral Ventricles: Although sudden collapse and overdistention of the lateral ventricles produced pain, direct stimulation of various parts of the ventricular walls (with their vessels as well as the choroid plexuses) did not result in pain. Specifically, it was found that coagulation, compression and faradic stimulation of the ependymal lining of the entire

lateral ventricle produced no pain. The large terminal vein which passes along the floor of the body of the lateral ventricle was insensitive to crushing, coagulation and faradic stimulation. The same was true for the choroid plexus at the glomus and in the region of the foramen of Monro. Spreading the lumen of the foramen of Monro and cutting its margins with the endothermy were painless. Firm pressure against the part of the ventricular wall nearest the thalamus was not followed by pain (4 subjects, 24 observations).

That a bilateral and diffuse type of headache resulted from rapid emptying or overdistention of the ventricular system was repeatedly

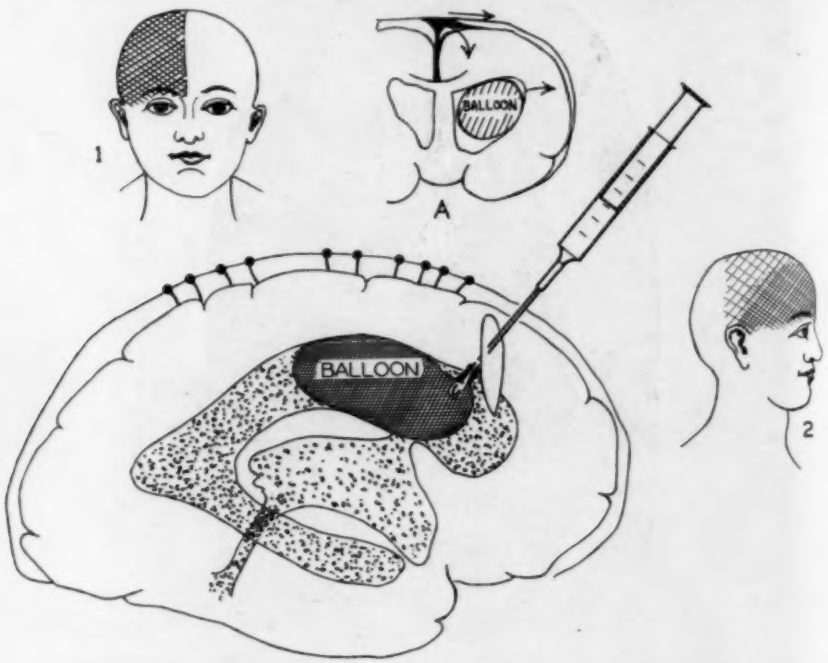

Fig. 16.—Schematic representation of a balloon in the lateral ventricle and the tributary veins passing from the cerebral cortex to the superior sagittal sinus. ● indicates the point at which the tributary veins were put on traction, causing pain with both inflation and deflation of the balloon. The insert (*A*) demonstrates the outward traction on the tributary veins, with inflation of the balloon, and the downward traction, with deflation. The diagrams, *1* and *2*, show the area of pain resulting from both distention and collapse of the body and frontal horn of one lateral ventricle.

demonstrated during ventriculographic studies. In the case of a tumor filling the third ventricle, the changes in pressure of the lateral ventricles alone produced the same type of pain.

A balloon placed through a small opening into the anterior horn and body of a lateral ventricle when inflated sufficiently to cause overdistention of the ventricle produced a diffuse frontal pain on the homolateral side of the head. This was done with the brain exposed, so that there was no possibility of stretching or compressing the dural arteries. Sudden deflation of the balloon produced a transitory and intense but poorly localized pain, again over the frontal area of the same side (figs. 15 and 16).

Third Ventricle: Manipulation of a paraphysial cyst lying in the third ventricle and traction and coagulation of its stalk in the region of the roof of the ventricle all were painless. The choroid plexus of this ventricle also was not sensitive to coagulation.

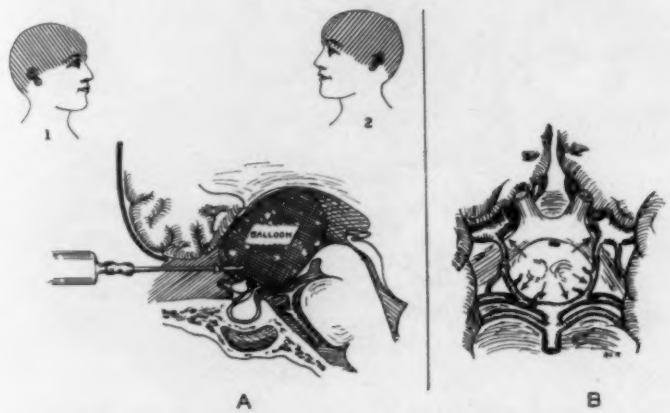

Fig. 17.—Schematic representation of (*A*) an inflated balloon in the third ventricle and (*B*) the resulting traction on pain-sensitive arteries of the circle of Willis. The arrows indicate the lines of force, with distention of the ventricular floor. Diagrams *1* and *2* show the diffuse area of pain following inflation of the balloon.

In a case of hydrocephalus due to obstruction of the aqueduct of Sylvius, an opening made into the third ventricle through the lamina terminalis was unaccompanied by pain. Cutting, crushing and coagulation of the ependyma of the ventricular wall here were painless. A balloon introduced into the third ventricle through this opening was inflated under moderate pressure and caused a diffuse pain over all parts of the head, variously said to be most intense in the back of the head, in the forehead and eyes and in the ears. Release of the pressure was accompanied by prompt cessation of the pain. In this respect it was unlike the pain which came with both distention and deflation of the balloon in the lateral ventricle. Pressure from the inside on the floor of the third ventricle, behind the chiasma, produced pain of similar

distribution and nature to that following distention of the ventricle, yet cutting and stretching of the floor alone in this region produced no pain. The conclusion was that the pain accompanying distention of the ventricle was due to traction by displacement of the large arteries in the region of the circle of Willis (fig. 17).

Aqueduct of Sylvius: The ependymal walls of the aqueduct were found to be insensitive when a snugly fitting catheter was used to stimulate them by pressure, stretching and traction. All parts of the walls of the aqueduct from the fourth to the third ventricle (fig. 18) were thus explored (1 subject, 4 observations).

Fig. 18.—View showing the aqueduct of Sylvius, the fourth ventricle, the choroid plexus and the cisterna magna. ○ indicates the point of stimulation without pain.

Fourth Ventricle: The ependymal walls of this ventricle lack sensitivity to pain just as do those of the other ventricles. It was found that cutting, coagulating and faradizing the roof of the ventricle caused no pain. Manipulation, traction and stroking of the floor of the ventricle likewise was painless (4 subjects, 16 observations). The choroid plexuses of this ventricle (fig. 18) were insensitive to coagulation, crushing, traction and faradic stimulation (4 subjects, 16 observations).

COMMENT

This study does not purport to determine whether structures found to be sensitive to pain on stimulation actually possess sensory endings or are only traversed by pain-conducting fibers. This differentiation is

difficult at best even with histologic methods, and conclusions must be deferred. Thus McNaughton,[6n] who failed to find nerve endings in the walls of venous sinuses in man, indicated that the question of their presence "may well be a problem of adequate staining methods." Also, it is conceivable that the methods of stimulation employed may not have been adequate in every instance to stimulate sensory endings for pain. In this respect a specific instance, particularly important to consider, is that of the pial arteries over the convexity of the hemispheres, which were found to be insensitive. It may be that the stimulus used was inadequate at one point or was not widespread enough to stimulate sparsely distributed end organs.

1. *"Pain Pathways" of the Head.*—The sensory innervation of the extracranial structures will not be considered here. A discussion of the innervation of pain-sensitive intracranial structures readily falls into a consideration of (*a*) the structures supplied by the fifth cranial nerve and (*b*) those supplied by other nerves. The fifth [4] and the tenth cranial nerves are widely conceded to be the principal afferent nerves of the intracranial structures, but, in addition, the ninth, eleventh and twelfth cranial [8] and the upper cervical nerves [4] play a role, as, perhaps, do other cranial nerves as well.

a. The sensory fibers of the fifth nerve supply the superior surface of the tentorium cerebelli and all the pain-sensitive structures that lie above it. The subtentorial structures probably receive few, if any, fibers from the fifth nerve.

Many fibers of the fifth nerve accompany the middle meningeal artery and its branches. The "nervus spinosus" described by Luschka [8c] as a branch of the third division and the "nervus meningeus medius" described by Arnold [9] as a branch principally of the second division of the trigeminal nerve are fairly constant. But McNaughton [6n] has indicated that there are also fine unnamed branches of all divisions of the fifth nerve accompanying the artery. It is hardly possible or even necessary to attempt to allocate all of these fine connections to one of the three divisions; suffice it to say that they are all components of the fifth nerve.

The nerve fibers follow the main divisions of the middle meningeal artery and form a network in the adventitia. Branches of the nerves

8. (*a*) Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du système grand sympathique, Paris, Gaston Doin & Cie, 1927. (*b*) Pearson, A. A.: The Hypoglossal Nerve in Human Embryos, J. Comp. Neurol. **71**:21, 1939. (*c*) von Luschka, H.: Die Nerven in der harten Hirnhaut, Tübingen, H. Laupp, 1850. Fay.[6g]

9. Arnold, F.: Handbuch der Anatomie des Menschen, Freiberg, A. Emmerling and Herder, 1851.

have been seen to extend out into the dura, away from the artery. The failure to find the dura itself sensitive to pain suggests that either the nerve fibers and endings are sparsely distributed or that such nerves as the dura possesses include no pain-conducting fibers. The nerves diminish in number as the vessels divide, but occasionally arteries of small caliber near the sagittal sinus have been found sensitive to pain. It is likely that some of the fibers extend even to the sagittal sinus and form a part of its sensory supply, particularly in its middle third.

There is less certainty about the nerves to the anterior meningeal arteries and the dura of the anterior fossa, but it is probable that the anterior meningeal branch of the internal carotid artery is accompanied by fibers which connect directly with the first division of the fifth nerve, near the gasserian ganglion.[6n] It is also probable that the meningeal branches of the ethmoidal arteries are accompanied by nerves which pass through the cribriform plate as branches of the intraorbital portion of the ophthalmic nerve.[6n] Whereas the sensory tests indicate that the pain-conducting fibers accompanying the middle meningeal artery do not supply any part of the dura traversed by that artery, the facts that the dura of the floor of the anterior fossa is uniformly sensitive to pain and that the quality and site of reference of pain are identical suggest that it and its arteries have a common nerve supply.

The nervus tentorii, a branch of the first division of the trigeminal nerve, was first described by Arnold[9] in 1851, and its existence has been repeatedly verified since. This nerve is made up of afferent fibers from at least the posterior extent of the superior sagittal sinus, passing by way of the falx to join afferent fibers from the superior surface of the tentorium cerebelli, the superior walls of the transverse and the straight sinuses and the torcular Herophili. The collected fibers pass anteriorly from the margin of the tentorium, in or close to the sheath of the trochlear nerve,[6n] to join the first division of the fifth nerve about 1 cm. from its ganglion. The nervus tentorii, therefore, carries painful impulses from the general region of the posterior and medial aspects of the supratentorial fossa.

The same nerve (nervus tentorii) in all probability supplies the pain-sensitive venous tributaries from the parietal and occipital lobes to the venous sinuses, but by virtue of the different location of the pain following stimulation of the group of inferior cerebral veins that drain the temporal lobe it is suggested that these latter tributary veins have another innervation, perhaps from fibers that accompany the posterior branch of the middle meningeal artery.

The arteries of the brain, including the parenchymal branches and also the choroid plexuses, have been shown to be equipped with nerve

fibers and endings.[10] Even though Huber's [10b] original conception of the myelinated fibers as sensory and the unmyelinated as vasomotor must now be modified, it is conceivable that many of these are pain-conducting fibers. Under the conditions of these investigations, however, stimulation of the large arteries at the base of the brain and only the most proximal portions of their cerebral branches caused pain. The nerve plexuses about these larger arteries are said to have connections with various cranial nerves [11] (the third, the fifth, the sixth, the seventh, the eighth, the ninth, the tenth, the eleventh and the twelfth). It seems unlikely that all of these cranial nerves serve as pathways from the pain-sensitive vessels, but at present definite information about these afferent pathways for pain is limited.

Studies on experimentally induced "histamine headache" indicate that the fifth cranial nerve is undoubtedly the chief afferent nerve for headache arising from dilatation of the pial and cerebral arteries of the supratentorial fossae.[4] It is also clear that stimulation of the intracranial portion of the internal carotid artery, the proximal 1 or 2 cm. of the midcerebral and postcerebral arteries [12] and the anterior cerebral artery as far up as the genu of the corpus callosum results in pain in the region of the homolateral eye. Since the pain resulting from stimulation of these larger arteries of the forebrain is experienced in the region of the eye, there is further reason to assume that at least the major part of the innervation of these vessels is by the fifth cranial nerve.

b. The arrangement of nerves beneath the tentorium is more complicated, but a few inferences regarding pathways for pain seem justifiable. The ninth, tenth and eleventh cranial nerves were shown to be sensitive to pain on direct stimulation intracranially, and the pain was

10. (*a*) Gulland, L.: The Occurrence of Nerves on Intracranial Blood Vessels, Brit. M. J. **2**:781, 1898. (*b*) Huber, G. C.: Observations on the Innervation of the Intracranial Vessels, J. Comp. Neurol. **9**:1, 1899. (*c*) Stöhr, P.: Ueber die Innervation der Pia Mater und des Plexus Choriodens des Menschen, Ztschr. f. d. ges. Anat. **63**:562, 1922. (*d*) Hassin, G. B.: The Nerve Supply of the Cerebral Blood Vessels: Histologic Study, Arch. Neurol. & Psychiat. **22**:375 (Aug.) 1929. (*e*) Stöhr, P. J.: Nerves of the Blood Vessels, Heart, Meninges, Digestive Tract and Urinary Bladder, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, sect. 8, p. 383. (*f*) Penfield, W.: Intracerebral Vascular Nerves, Arch. Neurol. & Psychiat. **27**: 30 (Jan.) 1932. (*g*) Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, with Observations on Pial and Intracerebral Vascular Plexus, ibid. **28**:1257 (Dec.) 1932. (*h*) Clark, S. L.: Innervation of the Choroid Plexus and the Blood Vessels Within the Central Nervous System, J. Comp. Neurol. **60**:21, 1934.

11. Dowgjallo, N. D.: Beiträge zur Lehre von der Innervation des peripherischen Blutgefäss-systems, Ztschr. f. d. ges. Anat. (pt. 1) **97**:9, 1932. McNaughton.[6n]

12. Fay.[6g,o]

felt in the general region of the back of the head and subocciput; the twelfth cranial nerve is said to be similar in this regard.[6g] The studies with experimentally induced "histamine headache" indicate that the ninth and tenth cranial and upper cervical nerves are undoubtedly the chief afferents for headache resulting from dilatation of pial and cerebral arteries of the infratentorial fossa.[4] Further differentiation of the specific innervation of the structures is afforded by the observation that the area of pain following stimulation of the undersurfaces of the transverse sinus, the torcular Herophili, the straight sinus, the upper end of the occipital sinus and the dura in the region of the sigmoid sinus is largely in and behind the homolateral ear and in the same area after direct stimulation of the ninth and tenth nerves. Since in this region pain could not be elicited on stimulation of the aforementioned structures after section of the ninth and tenth cranial nerves, the deduction that these two cranial nerves include afferent fibers for pain from these structures is further supported.

Similarly, it is inferred that the upper cervical nerves possess fibers for pain from the lower part of the occipital sinus, the vertebral and posterior inferior cerebellar arteries, the posterior meningeal artery and the dura of the floor of the posterior fossa near the rim of the foramen magnum, since stimulation of the structures after section of the upper cervical nerves did not elicit pain.

Finally, it is to be emphasized that the innervation by sensory fibers of all the structures investigated is strictly unilateral. The line of demarcation is sharp, so that even structures in the midline have half their innervation from one side and half from the other.

2. *The Mechanisms of Headache.*—From these data, inferences concerning headache may be formulated. Inflammation, traction, displacement and distention of pain-sensitive structures are the disturbances primarily responsible for headache. It is noteworthy that as a source of pain the cranial vascular structures far outweigh in number and distribution all others. It is to be anticipated, therefore, that vascular structures will often be implicated. Yet it is obvious that no single structure or mechanism is entirely responsible for the headache. Hence, the following varieties of mechanisms are briefly presented.

a. Traction on veins that pass to the sagittal and transverse sinuses from the cerebral cortex results in a dull, aching pain over a wide area on the front, top and side of the head. Not only are most of these veins sensitive to pain at the site of juncture with the sinus, but secondary traction on the walls of the sinuses to which they are attached causes pain. Since many of these veins bridge a gap of 1 to 3 cm. between the cortex of the brain and the sinus, swelling of the brain puts them under tension. Hence, tumors of the brain may produce headache either by displace-

ment and direct traction on these veins or through secondary hydrocephalus. Unusually low intracranial pressure, e. g., after lumbar puncture, may similarly result in traction on the tributary veins, principally those to the sagittal sinus, and thus induce headache. Air in the subarachnoid spaces after pneumoencephalographic procedures may likewise produce headache by causing traction on these anchoring veins.

b. Traction on the middle meningeal arteries causes headache as far forward as the eye and as far back as the ear, depending on whether the stress is primarily on the more anterior or the more posterior branches. Dural, extradural or subdural tumors causing traction on these arteries in any part of their extent, from their origin at the foramen spinosum in the middle fossa to their terminal branches near the sagittal sinus, may thus cause headache.

c. Traction on the large arteries at the base of the brain and their main cerebral branches or on the pia-arachnoid in immediate contact with them causes headache. When the traction is on the intracranial portion of the internal carotid arteries and the major components of the circle of Willis the headache occurs in the region of the eyes or in the front, top or sides of the head. Traction on the basilar and vertebral arteries and their branches produces headache in the back of the head and neck. Displacement of this entire arterial system from right to left causes a generalized headache, chiefly on the right, from the eye to the neck. Distention of the third ventricle causes traction on numerous arteries at the base of the brain and results in pain all over the head (fig. 17). Tumors in the region of the sella turcica or above it may cause pain by traction on the pain-sensitive arteries at the anterior end of the circle of Willis. The anterior cerebral artery, when under traction even as high as the genu of the corpus callosum, causes pain over or within the eye. Hence, tumors in the frontal lobe or in the corpus callosum causing traction on one or both of these arteries may produce pain in the region of the eye as described.

Since traction on pontile and internal auditory arteries causes pain within and behind the ear, tumors of the eighth nerve and others within the cerebellopontile angle or in the region of the internal auditory meatus may cause pain in the region about the ear.

d. Distention and dilation of the intracranial and extracranial arteries results in headache (see introductory paragraph). The arteries responsible for such pain are: pial arteries (chiefly at the base, as has been described), dural arteries (chiefly the middle meningeal), a few superficial branches of the internal carotid artery and many branches of the external carotid artery on the front, side and back of the head. Five varieties of headache may result from dilatation and distention of cranial arteries: (1) headache resulting from chemical agents, such as histamine

or amyl nitrite;[13] (2) migraine headache;[14] (3) headache associated with fever or septicemia;[15] (4) headache associated with hypertension[3a] and (5) postconvulsive headache.

e. Inflammation involving the pain-sensitive structures at the base and the convexity of the brain causes severe headache. When inflammation is limited to the posterior fossa the headache is chiefly over the back of the head. When the inflammation is in the supratentorial fossa the headache is primarily frontal or vertical. The headaches associated with meningitis, subarachnoid hemorrhage or meningeal invasion by tumor are examples of headaches due to local tissue reaction or inflammation.

f. Direct pressure by tumors on nerves possessing many pain-conducting fibers may cause pain. Thus, compression of the intracranial portion of the sensory division of the fifth cranial nerve results in pain in the front, top and side of the face and head. Similarly, compression of the intracranial portions of the ninth and tenth cranial nerves produces pain in and behind the corresponding ear, while compression of the upper cervical roots results in pain in the back of the head and neck.

Tumors probably do not commonly cause headache through circumscribed pressure on the dura even in the pain-sensitive areas. Thus, mere downward pressure on the dura of the floor of the anterior fossa, for example, does not cause headache. Although neoplastic invasion of the dura with the usual inflammatory reaction may be a cause of headache, as has been mentioned, traction and displacement of arterial and venous structures are the mechanical disturbances more likely to be responsible for headache in the presence of a tumor.

Because of its importance, the headache associated with increased intracranial pressure will be further considered. It is unlikely from the data given earlier that mere pressure, local or general, will of itself give rise to the incapacitating headaches that sometimes accompany this state. Other forces associated with the increase in pressure are more significant. Traction on the tributary veins which act as anchoring structures for the brain may be evaluated first.[6h]

It has been shown that stretching the many tributary veins which pass from the cerebral cortex to the dural sinuses produces pain. Also because of the arrangement and location of these vessels, they are pulled on not only when the brain is edematous or distended by dilated ventricles but when it sags as a result of sudden withdrawal of cerebrospinal or ventricular fluid. This was demonstrated by placing a balloon in one lateral ventricle. In this experiment both the dilatation and the sudden collapse of the walls of one lateral ventricle produced homolateral

13. Leake and others.[1a] Hitz and Kammer.[1b] Pickering and Hess.[2a] Clark, Hough and Wolff.[2b]

14. Graham and Wolff.[5] Sutherland and Wolff.[3a]

15. Wolff.[1d] Sutherland and Wolff.[3a] Pickering.[3b]

headache. Under these circumstances distention or displacement of the third ventricle could be eliminated as a factor in production of the pain. Moreover, it is unlikely that the procedure produced enough obstruction of cerebral arterial flow to increase the tension of the walls in the large arteries at the base.

Second, headache occurring during increased intracranial pressure may result from traction on the large pial and cerebral arteries at the base of the brain and the proximal portions of their more immediate branches. The pain associated with dilatation of the third ventricle is an example of such a mechanism in operation.

Third, headache may result from traction on the middle meningeal artery, secondary to the stretch of the tightly drawn dura over the convexity of the cerebral hemispheres.

Still another mechanism that deserves consideration is herniation of the cerebellum into the foramen magnum during increased intracranial pressure. The protrusion of the tonsils and vermis of the cerebellum into the foramen magnum (during increased intracranial pressure) not only may put traction on the occipital sinus but may displace or stretch the upper cervical posterior roots. This would result in occipital headache secondary to direct pressure on nerves possessing many pain-conducting fibers, that is, the sixth mechanism described in the foregoing paragraphs.

Northfield,[91] in his explanation of headache from increased intracranial pressure due to ventricular block, parenchymal tumor or edema, advanced the view that headache "is due to some disturbance of the tension of the walls of the cerebral vessels and it is this disturbance of tension which provides the adequate stimulus for the excitation of pain." He compared the headache resulting from histamine with that resulting from increased intracranial pressure and assumed that in the case of both, dilatation of the pial arteries is responsible for the pain. This argument is based in part on the observation made on animals that a gradual increase in intracranial pressure produces dilatation of the arteries and veins over the cerebral convexity.[16] The mechanism of this vasodilatation has never been conclusively defined, but it is probably comparable to the cerebral vasodilatation associated with a slower blood flow following a fall in blood pressure or to the dilatation following inhalation of carbon dioxide.[17] Vasodilatation of this magnitude may produce headache. It is therefore conceivable that headache associated with increased intracranial pressure could in part originate in this manner. It is probable, however, that such vasodilatation alone is less

16. Wolff, H. G., and Forbes, H. S.: The Cerebral Circulation: V. Observations of the Pial Circulation During Changes in Intracranial Pressure, Arch. Neurol. & Psychiat. **20**:1035 (Nov.) 1928.

17. Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545, 1936.

important as a mechanism for headache during increased intracranial pressure than is traction on pain-sensitive arteries and veins. Certainly these factors may combine.

Elsberg [6e] suggested that "sudden changes in pressure conditions within the third ventricle and on the optic thalami that form its lateral walls may be a factor in some varieties of headache." The choroid plexuses, vessels and ependymal walls of the entire ventricular system have been demonstrated to be insensitive to various forms of direct stimulation, and, in addition, the thalamus has been pressed on through the floor of the lateral ventricle without producing pain. Therefore, whatever pain results from changes in intraventricular pressure probably is due to secondary stimulation of the more remote structures mentioned in the previous paragraphs.

3. *Headache and Referred Pain.*—Referred pain is loosely defined as any pain which is felt at a site other than that of stimulation. Some prefer to limit the term to those distant pains that are accompanied by paresthesias and increased sensitivity of the skin at the site of reference. In this discussion referred pain will be used in the broader sense, to indicate pain both with and without increased sensitivity of the skin.

a. Headache and Referred Pain from Intracranial Structures: Because of the uniformity of response in the location of pain following stimulation of pain-sensitive intracranial structures, the following generalization is justified. Pain in front of a line drawn vertically from the ear indicates that a pain-sensitive structure of the superior surface of the tentorium (or above) is being stimulated; pain behind this line implies stimulation of a pain-sensitive structure beneath the tentorium.

It has been maintained that when referred pain is associated with "tenderness" of the skin, local infiltration of procaine hydrochloride not only decreases this local sensitivity but abolishes the referred pain.[18] The local sensitivity is decreased by infiltration with this anesthetic, but it has never been possible to eliminate headache or, indeed, to prevent the onset of the headache associated with pneumoencephalography or such agents as histamine by such infiltration.[4]

The following summary is a correlation of intracranial structures and the location of pain resulting from stimulation of these structures.

The structures which when stimulated give rise to pain in the general region of the eye and forehead are: the dura of the anterior fossa; the anterior meningeal arteries; the structures innervated by the tentorial nerve (which include the superior surfaces of the tentorium, torcular Herophili, transverse and straight sinuses, the sagittal sinus in its posterior half and various tributary veins to these sinuses); the sylvian vein; the intracranial portion of the internal carotid artery; the vessels of the circle of Willis and the proximal portions of the larger cerebral branches, and the first division of the fifth nerve.

18. Weiss, S., and Davis, D.: The Significance of Afferent Impulses from the Skin and the Mechanism of Visceral Pain, Am. J. M. Sc. **176**:517, 1928.

The structures which when stimulated give rise to pain felt in the temporal and parietal regions of the head are: the middle meningeal arteries; the inferior cerebral veins of the temporal lobe that connect with the venous sinuses, and the anterior portion of the sagittal sinus and its venous tributaries. In the temporoparietal region there is even more discrete localization, because stimulation of the more proximal parts of the midmeningeal arteries causes pain at a lower level than does stimulation of the more distal parts of these vessels.

When parietal pain is produced by stimulation of the midportion of the sagittal sinus and its tributaries it is localized near the vertex. Traction on the floor of a sella turcica containing a pituitary adenoma that had broken through the roof of the sphenoid sinus caused pain in the vertex. It was inferred that the mucous membrane of the sphenoid sinus and not the dura of the sella was the structure responsible for this pain.

The occipital and suboccipital regions of the head comprise even a smaller combined area than the frontoparietotemporal region, and localization of pain to any specific part of this posterior area is overprecise. Yet some structures in the posterior fossa are responsible for pain near the midline of the skull and in the upper cervical regions only, and other structures are responsible for pain in or behind the ear. The intracranial structures which when stimulated give rise to pain in or behind the ear are: the undersurface of the walls of the torcular Herophili, the straight sinus and the transverse sinus; the walls of that half of the occipital sinus nearest the torcular; the wall of the sigmoid sinus and dura adjacent to it; the pontile and the internal auditory arteries, and the intracranial portions of the ninth and tenth cranial nerves. Stimulation at widely separated points along the transverse sinus results in separately localized pain within a comparatively small region on a line between the ear and the occipital protuberance.

The intracranial structures which when stimulated give rise to pain in the occiput (near the midline) and in the upper cervical region include the lower half of the occipital sinus and its branches at the margin of the foramen magnum; that part of the dura of the floor of the posterior fossa not covering or adjacent to the sigmoid sinus; the posterior meningeal arteries; the proximal portion of the posterior inferior cerebellar artery; the vertebral artery; the basilar artery, and the intracranial portions of the eleventh and possibly the twelfth cranial nerves.

Pain in the back of the head and neck without the more specific localizations mentioned results from stimulation of the posterior roots of the upper cervical nerves.

Persons with intracranial lesions which produce localized headache often have a perversion of sensation to superficial stimuli in that region.[19] The response to stimulation with cotton, pressure and pinprick in the region is in the nature of a paresthesia with hypersensitivity or hyperalgesia. Therefore, it is conceivable that an area of such perversion of sensation might help to fix the site of an intracranial disease process, be it a tumor, a hematoma, inflammation or a scar. In actual experience, it is found that the test is sometimes useful when dealing with lesions that are on or near the surface of the brain and impinge directly on pain-sensitive structures. Brief histories of 2 patients will serve as examples.

19. Lewy, F. H.: The Localization of Intracranial Lesions, Ann. Surg. **109**: 28, 1939.

CASE 1.—A 28 year old woman had the single complaint of persistent pain just behind the left ear for two years. On examination there were diminished corneal sensation on the left and slight incoordination of movements on the left side of the body. Pressure, touch and pinprick on the scalp in a localized region behind the left ear resulted in a paresthesia or in hyperalgesia. At operation a left acoustic neurinoma was found.

Since the observations on sensitivity to pain in the posterior fossa indicate that stimulation of the dura in the region of the cerebellopontile angle, the wall of the sigmoid sinus, the pontile artery and the internal auditory artery produces pain exclusively in the region just behind the ear, it is reasonable to conclude that some or all of these structures were irritated by the tumor, which gave little additional clue to its presence.

CASE 2.—A 50 year old man was admitted to the hospital in stupor which had become deeper after a series of short, generalized convulsive seizures six hours before. An unreliable history disclosed only the complaint of moderate headache for the preceding few months. The meager collection of abnormalities detected on examination suggested a lesion of the left hemisphere, but pressure over the right parietal region of the head caused much greater discomfort than pressure elsewhere. Operative exposure revealed a parietal subdural hematoma on the right.

Observations on sensitivity to pain have indicated that the principal intracranial structures responsible for pain in the parietal region are the middle meningeal artery and the more anterior portion of the wall of the sagittal sinus with its venous tributaries. It is reasonable to conclude that in this case one or all of these structures were stimulated by the hematoma.

In brief, unilateral hyperalgesia localized in the parietal area may indicate the presence of a lesion in the region of the middle meningeal artery, and hyperalgesia localized in the postauricular region may indicate the presence of a lesion in the region of the internal auditory meatus. On the other hand, areas of local hyperalgesia can be relied on to indicate the location of the lesion only when the lesion produces direct stimulation of a pain-sensitive structure. Even then an area of hyperalgesia above the eye, for instance, would not help one distinguish between lesions as remotely separated as those on the dura of the floor of the anterior fossa or on the supratentorial wall of the torcular Herophili.

Subcortical cerebral tumors which produce headache and areas of paresthesia and hyperalgesia do so only by distant and indirect effects on pain-sensitive structures. Cerebellar tumors commonly produce, besides pain in the back of the head, pain and tenderness over the eyes. Some have attributed the frontal pain to pressure of the tumor on the tentorium, but our observations have shown that pressure on the undersurface of the tentorium, greater than would result from any tumor, is required to produce pain in the frontal region. A more cogent explanation for pain and hyperalgesia of the frontal region in cases of cerebellar tumor is

the tension on tributary veins of the supratentorial sinuses that would inevitably result from the hydrocephalus. The following case will serve to illustrate the point.

CASE 3.—A 12 year old girl was admitted to the hospital. The complaints were of frontal, occipital and suboccipital headache and recurrent attacks of vomiting for seven months. There was hyperalgesia of the scalp just above the right eye and in both suboccipital regions; there were markedly choked disks and slight nystagmus but no other localizing signs of a tumor. A preoperative diagnosis of cerebellar tumor was made, and ventriculographic examination showed symmetric dilatation of the lateral and third ventricles, with the fluid under increased pressure. Operation disclosed a benign obstruction of the aqueduct of Sylvius.

In this instance the areas of headache and abnormal sensory perception in the scalp were definite and were similar to those encountered in patients with cerebellar tumors. The observations made at operation proved that the pain did not result from any local effects of the lesion but only from the indirect effects of hydrocephalus on many pain-sensitive structures in both the supratentorial and the infratentorial fossae.

Thus, it is evident that local tenderness of the scalp serves as an index to the structures responsible for pain but cannot be relied on implicitly to localize the lesion that initiates the stimulus, especially in the presence of hydrocephalus and generalized increase in intracranial pressure.

b. Headache and Referred Pain from Extracranial Structures of the Head and Neck: Pain that has its origin in the extracranial structures of the head occurs mostly at or near the site of stimulation. Yet, if intense enough, the pain which arises in any structure of the head, such as the skin and arteries of the head and face,[20] the mucus membranes of the mouth, the eyes or the teeth, may spread to other parts of the head innervated by the same division or other divisions of the fifth cranial nerve. Similarly, intense pain arising in the neck from such structures as the skin, arteries [20] and muscles may spread from one cervical segment to the next and thus be felt over the occiput as high as the vertex. The special sites of reference of pain from the paranasal sinuses are under investigation.

c. Headache and Referred Pain from Thoracic, Abdominal and Pelvic Viscera: Referred pain implies intimate anatomic connection between the site stimulated and the site at which pain is felt, even though these two regions are topographically widely separated. Headache as referred pain from intracranial structures and even from extracranial structures of the head and neck presents no difficulties, since pain is felt in that area on the surface which is supplied by the same nerve as the

20. Fay,[6g] Sutherland and Wolff.[3a]

structures stimulated. Headache in association with dysfunction of other parts of the body, however, not only is more complicated but seldom is referred pain.

In order to separate the headaches that actually are referred pain from those that are not, further consideration of the features which characterize referred pain is desirable. First, referred pain and the associated paresthesia of the skin need not be diffused over all parts of that segment to which it is referred but may be experienced in a part of the dermatome. Second, if the intensity of the afferent impulses from the stimulated site is great enough, the pain and paresthesia may spread from one segment to that immediately adjoining it; such spread may include the corresponding segments on the opposite side of the body. Third, the spread of pain from one segment to another is progressive and orderly, so that intense pain may be experienced far from the segment in which it begins. One may observe from the account of the progression or find at the time of examination that pain and perhaps paresthesia are still present in the intermediate segments even though the complaint is centered on the more remote segments.

Headaches that are referred pain from sources other than the head do occur and have the aforementioned distinguishing features but are indeed rare. Coronary occlusion is sometimes associated with such headaches. The pain of coronary occlusion may begin over the precordium and spread to the fifth finger and in succession to the other fingers of the hand, up the neck to the angle of the jaw and back teeth and over the back of the head as high as the vertex.

The extent of the spread of pain depends on the intensity of the pain, and the more intense the pain the greater is the spread. The severe pain of gallbladder and renal colic, therefore, may sometimes spread to the head, but such headache is exceedingly rare.

There is often confused with the limited variety of referred headache just described an entirely different category of headache, to be mentioned here only for clarification. Thus, when thoracic, abdominal, pelvic or any systemic disease is associated with fever or sepsis, headache usually results. It has been shown that headaches associated with these states are caued by dilatation of the cerebral arteries [3a] and that the site of origin of the sepsis has no bearing on the degree or site of the vasodilatation or the location of the headache. In the light of these new data it is relevant to consider the often cited instances of headache resulting from thoracic disease described by Head.[21]

Head maintained that disease of the structures innervated by thoracic segments is commonly associated with headache of specific localization.

21. Head, H.: On Disturbance of Sensation, with Especial Reference to the Pain of Visceral Disease, Brain **17**:339, 1894.

He cited as evidence that disease of the tenth thoracic segment is associated with headache over the occiput; disease involving the eighth thoracic segment, with headache of the vertex; disease involving the seventh thoracic segment, with headache in the temporal region, and disease involving the sixth thoracic segment with headache over the eyes and temples. When the cases presented as evidence for his thesis are analyzed, it is seen that the patient with headache associated with disease of the tenth thoracic segment was suffering from bacterial endocarditis with lesions of the aortic and mitral valves. The patient with disease involving the eighth thoracic segment had pulmonary tuberculosis with fever. The patient with disease involving the seventh thoracic segment had a severe anemia and gastralgia. The patient with disease involving the sixth segment had rheumatic endocarditis with aortic stenosis.

The incidence of fever and sepsis in these patients is to be noted. The headache was constantly experienced by Head's patients in this or that portion of the head in connection with one or another thoracic segment, but this has not been noted with our patients. On the other hand, it was usual to find the headache predominantly in the temporal, parietal, vertical or occipital regions in different patients at different times.

SUMMARY AND CONCLUSIONS

The sensitivity to pain of the tissues covering the cranium, the cranium itself and most of the intracranial structures has been ascertained from a series of 30 patients [7] during surgical procedures on the head. Some of the "pain pathways" and the mechanisms of headache are defined.

The use of a variety of stimuli has resulted in the following conclusions about the sensitivity to pain of the structures investigated:

1. Of the tissues covering the cranium, all are more or less sensitive to pain, the arteries being especially so.

2. Of the intracranial structures, the great venous sinuses and their venous tributaries from the surface of the brain, parts of the dura at the base, the dural arteries and the cerebral arteries at the base of the brain are sensitive to pain.

3. The cranium (including the diploic and emissary veins), the parenchyma of the brain, most of the dura, most of the pia-arachnoid, the ependymal lining of the ventricles and the choroid plexuses, are not sensitive to pain.

With the exception of those sensations that resulted from stimulation of the parenchyma and nerves, the only sensation that was experienced on stimulation of the intracranial structures was pain.

Stimulation of the pain-sensitive intracranial structures on or above the superior surface of the tentorium cerebelli resulted in pain in various

regions in front of a line drawn vertically from the ears across the top of the head. The pathways for this pain are contained in the fifth cranial nerve.

Stimulation of the pain-sensitive intracranial structures on or below the inferior surface of the tentorium cerebelli resulted in pain in various regions behind the line just described. The pathways for this pain are contained chiefly in the ninth and tenth cranial nerves and the upper three cervical nerves.

From the data available, six basic mechanisms of headache have been formulated. Headache may result from (1) traction on the veins that pass to the venous sinuses from the surface of the brain and displacement of the great venous sinuses; (2) traction on the middle meningeal arteries; (3) traction on the large arteries at the base of the brain and their main branches; (4) distention and dilatation of intracranial and extracranial arteries; (5) inflammation in or about any of the pain-sensitive structures of the head, and (6) direct pressure by tumors on the cranial and cervical nerves containing many pain-afferent fibers from the head.

Intracranial diseases commonly cause headache through more than one of these mechanisms and by involvement of more than one pain-sensitive structure. Traction, displacement, distention and inflammation of cranial vascular structures are chiefly responsible for headache.

Headache from intracranial disease is usually referred pain. Local tenderness of the scalp may serve as an index to the structures responsible when a lesion produces direct irritation of pain-sensitive structures. Since disease of remotely separated pain-sensitive structures may cause pain and hyperalgesia in identical areas, the clinical usefulness of such localization is limited. But unilateral hyperalgesia localized in the parietal area indicates the possibility of a lesion near the middle meningeal artery, and hyperalgesia localized to the postauricular region indicates the possibility of a lesion in the region of the internal auditory meatus.

Many of the anatomic drawings accompanying this paper are based on illustrations in the publication of Northfield [61] and in the following textbooks on anatomy: Toldt, C.: Anatomischer Atlas, edited by F. Hochstetter, ed. 17, Berlin, Urban & Schwarzenberg, 1937. Morris, H.: Human Anatomy, edited by C. M. Jackson, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1923. Bourgery, J. M.: Traité complet, de l'anatomie de l'homme, Paris, C. A. Delaunay, 1840. Spalteholz, K. W.: Hand Atlas of Human Anatomy, translated from the seventh German edition by L. F. Barker, ed. 4, Philadelphia, J. B. Lippincott Company, 1923. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 23, Philadelphia, Lea & Febiger, 1936. Sobotta, J.: Atlas of Human Anatomy, edited from the sixth German edition of J. P. McMurrich, New York, G. E. Stechert & Company, 1930.

Miss Helen Goodell helped in the preparation of the manuscript and the drawings.

DIRECT INGUINAL HERNIAS

A STUDY OF SIX HUNDRED AND FIVE HERNIAS AND OF FIVE HUNDRED AND SIXTY-FIVE REPAIRS

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This study covers 605 direct inguinal hernias, none of which had been operated on previously.[1] Included were all direct hernias in patients admitted to the wards at St. Luke's Hospital, New York, from 1926 to 1935 inclusive, and all repairs of direct inguinal hernias from 1916 to 1925 inclusive, subsequently observed for nine months or longer. Of the 605 hernias, 565 were repaired. Among the latter, 458 were followed for nine months or longer. Sixty-eight recurrences were discovered, giving a recurrence rate of 14.8 per cent. The average follow-up time was thirty-three and two-tenths months. The average time after operation at which the recurrences were discovered was twenty-six months.

These direct hernias comprised 13.6 per cent of all hernias and 16.6 per cent of all inguinal hernias included in the study as outlined in the foregoing paragraph.

ETIOLOGIC FACTORS

Onset (Age at Which Hernias Were First Noted).—Only 2 per cent of these hernias were first noted during the first twenty years of life. Included in the five year period from the twentieth to the twenty-fifth year of life was the smallest percentage of hernias, 6.8 per cent, found in any five year group from 20 to 55 years of age. The percentages noted in the five year periods from 25 to 55 years were relatively equal. The highest incidences were in the fifth decade of life, both five year groups showing 15.9 per cent of the hernias in this entire group. From the fifty-fifth year on, each successive group showed a marked decrease in incidence. The average age of the patients when these direct inguinal hernias were first noted was 40.8 years. This is ten years later in life than was the case with incomplete indirect inguinal hernias.

The incidences of recurrence were fairly evenly spread over the five year periods from the age of 30 years on. When the patients were

From the Surgical Services of St. Luke's Hospital.

1. All figures in regard to incomplete and complete indirect inguinal hernias in this paper are from the following two papers published by me: Incomplete Indirect Inguinal Hernias: A Study of 2,462 Hernias and 2,337 Repairs, Arch. Surg. **41**:747-771 (Sept.) 1940; Complete Indirect Inguinal Hernias: A Study of 305 Hernias and Repairs, South. Surgeon **9**:257-268 (April) 1940.

under 25 years of age at the time these hernias were first noted, no recurrences were found following the repair. In patients between the ages of 20 and 40 years when the hernias were first noted the recurrence rate was 14.5 per cent; in patients 40 to 60 years old, 15.0 per cent, and in patients 60 to 80 years old, 23.8 per cent.

Age at Time of Admission or Operation.—Few of these hernias (1.1 per cent) were repaired surgically in patients under 20 years of age. Only 3.5 per cent were repaired in patients between the ages of

TABLE 1.—*Age at Which Hernia Was First Noted*

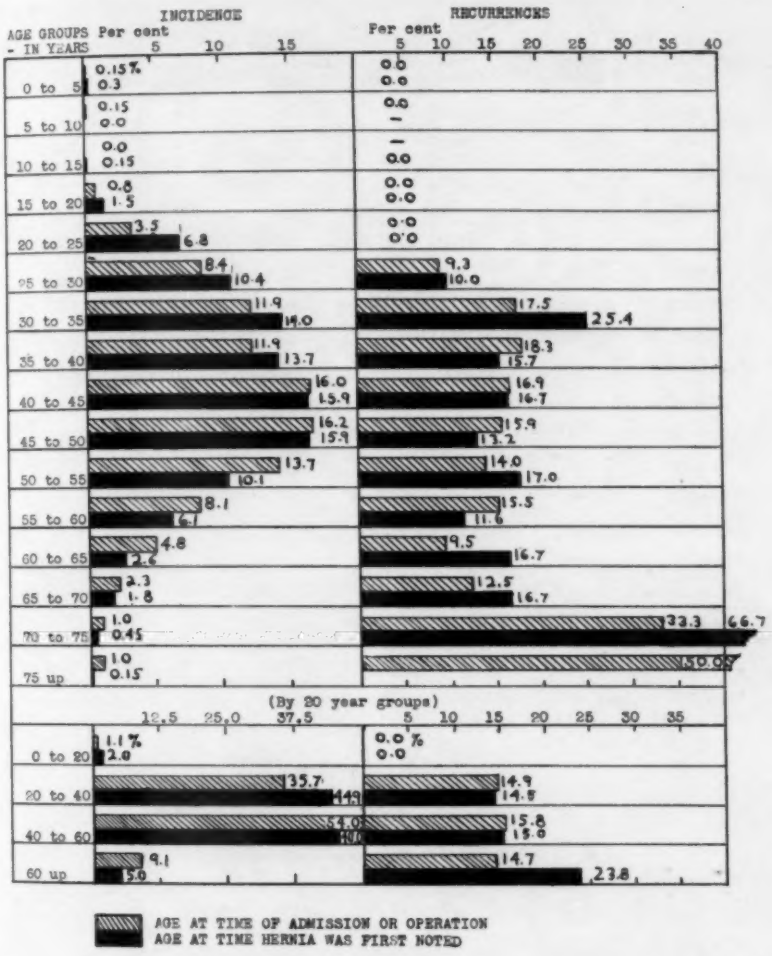
Age Group, Years	Total Hernias	Per Cent of Entire Group		Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	
0 to 5	2	0.3	2.0	2	0	0.0	0.0
5 to 10	0	0.0		..	..	...	
10 to 15	1	0.15		1	0	0.0	
15 to 20	9	1.5		8	0	0.0	
20 to 25	41	6.8	44.9	34	0	0.0	14.5
25 to 30	63	10.4		50	5	10.0	
30 to 35	85	14.0		59	15	25.4	
35 to 40	83	13.7		70	11	15.7	
40 to 45	96	15.9	48.0	72	12	16.7	15.0
45 to 50	96	15.9		68	9	13.2	
50 to 55	61	10.1		47	8	17.0	
55 to 60	37	6.1		26	3	11.6	
60 to 65	16	2.6	5.0	12	2	16.7	23.8
65 to 70	11	1.8		6	1	16.7	
70 to 75	3	0.45		3	2	66.7	
75 to 80	1	0.15		0	..	....	
Totals.....	605	100.0	100.0	458	68	14.8	14.8

The average age of the patients when direct inguinal hernias were first noted was 40.8 years.

20 and 25 years, and but 4.6 per cent in all before the twenty-fifth year of life. The age incidence at the time of admission to the hospital or operation increased up to the five year period from 45 to 50 years, with an incidence of 16.2 per cent. Each successive five year group following the fiftieth year of life showed a marked decrease. Throughout, greater percentages of patients were found in the more advanced age groups at the time of admission or operation as compared to the corresponding figures for incomplete indirect inguinal hernias, the average age for the former being 43.7 years and for the latter 34.8 years.

No recurrences were found following repairs of direct inguinal hernias performed on patients under the age of 25 years. The recur-

rence rate was 9.3 per cent for the age group 25 to 30 years. The incidences of recurrence were roughly the same in the various five year periods from 30 to 70 years. Beyond the latter age the numbers of followed repairs were too small to give significant recurrence rates.



Age incidence.

The percentages of recurrence in the twenty year groups from the age of 20 years on were essentially the same for each group, varying only from 14.7 to 15.8 per cent. Apparently, the age of the patients at the time their direct hernias were repaired had little effect on the expectation of recurrence.

Sex.—A great majority of these hernias occurred in males, 96.9 per cent. This compared with 88.7 per cent of incomplete indirect inguinal hernias. Only 3.1 per cent were found in females, which is about

TABLE 2.—*Age at Time of Admission or Operation*

Age Group, Years	Total Hernias	Per Cent of Entire Group		Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	
0 to 5	1	0.15	1.1	1	0	0.0	0.0
5 to 10	1	0.15		1	0	0.0	
10 to 15	0	0.0		..	..	....	
15 to 20	5	0.8		5	0	0.0	
20 to 25	21	3.5	35.7	15	0	0.0	14.9
25 to 30	51	8.4		43	4	9.3	
30 to 35	72	11.9		57	10	17.5	
35 to 40	72	11.9		60	11	18.3	
40 to 45	97	16.0	54.0	71	12	16.9	15.8
45 to 50	98	16.2		69	11	15.9	
50 to 55	83	13.7		57	8	14.0	
55 to 60	49	8.1		45	7	15.5	
60 to 65	29	4.8	9.1	21	2	9.5	14.7
65 to 70	14	2.3		8	1	12.5	
70 to 75	6	1.0		3	1	33.3	
75 to 80	4	0.7		2	1	50.0	
80 to 85	2	0.3		0	..	....	
Totals.....	605	100.0	100.0	458	68	14.8	14.8

The average age of the patients at the time of admission to the hospital or operation for direct inguinal hernias was 43.7 years.

TABLE 3.—*Sex*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Male.....	586	96.9	440	67	15.2
Female.....	19	3.1	18	1	5.5
Totals.....	605	100.0	458	68	14.8

one fourth of the incidence of incomplete indirect inguinal hernias in females.

The recurrence rate for males, 15.2 per cent, was double that for males after repairs of incomplete indirect inguinal hernias. The recurrence rates for these two types of hernia in females were essentially the same, for direct hernias 5.5 per cent and for incomplete indirect inguinal hernias 4.9 per cent.

Race.—The division of these hernias according to the race of the patients was essentially the same as that found in the study of incomplete indirect inguinal hernias, as follows: white patients, 94.7 per cent; Negroes, 5 per cent, and yellow patients, 0.15 per cent. These figures corresponded closely to the racial proportions among the general admissions to the hospital.

Trauma.—A history of definite trauma as the etiologic factor in the development of their direct inguinal hernias was given by 31.4

TABLE 4.—*Race*

Race	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
White	574	94.7	433	65	15.0
Negro	30	5.0	24	3	12.5
Yellow	1	0.15	1	0	0.0
Totals	605	100.0	458	68	14.8

TABLE 5.—*History of Definite Trauma as Etiologic Factor* *

History of Trauma	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Absent	415	68.6	322	50	15.5
Positive *	190	31.4	136	18	13.2
Totals	605	100.0	458	68	14.8

* Undoubtedly all or a major part of these hernias were present before the incidence of the trauma, which served only to call the patients' attention to the presence of the hernia. In this connection it is interesting to note that among the 305 complete (congenital) indirect inguinal hernias studied, a history of definite trauma as the etiologic factor in the development of their hernias was given by 26 per cent of the patients who first noted their hernias after the age of 15 years (Shelley, H. J.: Complete Indirect Inguinal Hernias: A Study of 305 Hernias and Repairs, South. Surgeon **9**: 257-268, 1930).

per cent of the patients, as compared to 26.7 per cent of the patients with incomplete indirect inguinal hernias (see note under table 5).

The proportionate decrease in the incidence of recurrence among patients giving a history of trauma as the etiologic factor was not as definite as with incomplete indirect inguinal hernias. With no history of trauma, the incidence of recurrences was 15.5 per cent, as compared to 13.2 per cent when such a history was given.

SYMPTOMS

Pain.—A slightly greater percentage of these patients gave a history of pain associated with their direct inguinal hernias than was noted with incomplete indirect inguinal hernias (52.2 per cent of the former and 49.7 per cent of the latter).

Duration.—The average elapsed time from discovery of these hernias to the patient's admission to the hospital or repair was one year less than the corresponding figure for incomplete indirect inguinal hernias. The average duration, as defined in a foregoing section, was two and nine-tenth years for the former as compared to three and nine-tenths years for the latter.

The length of time for which the patients had had their direct inguinal hernias before operative repair apparently had little effect, if any, on the recurrence rate.

TABLE 6.—*History of Pain Associated with Hernia*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	289	47.8
Positive	316	52.2
Total	605	100.0

TABLE 7.—*Duration (Time Hernia Was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
To 1 week	74	12.2	60	8	13.3
To 1 month	143	23.6	110	16	14.5
First 6 months	270	44.6	204	30	14.7
Second 6 months	65	10.7	57	9	15.8
To 1 year	335	55.4	261	39	14.9
0 to 5 years	463	76.5	363	59	16.3
5 to 10 years	74	12.2	49	4	8.2
0 to 10 years	537	88.8	412	63	15.3
10 to 20 years	47	7.8	31	4	12.9
20 to 30 years	20	3.3	14	1	7.1
30 to 40 years	1	0.15	1	0	0.0
Totals	605	100.0	458	68	14.8

The average duration (time elapsed from discovery to time of admission or operation) for direct inguinal hernias was 2.9 years.

PHYSICAL FINDINGS

Size.—As compared to the findings with incomplete indirect inguinal hernias, the incidence of direct inguinal hernias with the sac of such a size that it was contained entirely in the inguinal canal was one fourth greater, 32.6 per cent for direct hernias and 26.7 per cent for incomplete indirect hernias. The percentage of hernias which extended beyond the external ring but not into the scrotum was slightly more than one third greater in the case of direct hernias, 55 per cent compared to 40.7 per cent. In contrast to these increases in incidence, scrotal hernias

showed an incidence of only slightly more than one third that found with incomplete indirect inguinal hernias, 12.4 per cent compared to 32.6 per cent.

The incidences of recurrence for the two groups in which the sac extended just beyond the external ring or into the scrotum were more

TABLE 8.—*Size*

Size of Hernia †	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Size I	197	32.6	146	12	8.2	0 in 106 operations	0.0
Size II	333	55.0	259	45	17.4	1 in 163 operations	0.6
Size III	75	12.4	53	11	20.9	1 in 43 operations*	2.3
Totals	605	100.0	458	68	14.8	1 in 312 operations*	0.32

* The single death was due to a volvulus which developed after operative reduction and repair of a strangulated hernia. The strangulation developed in an old incarcerated hernia.
† Size I: Hernias in which the sac was limited in extent to the inguinal canal.
Size II: Hernias in which the sac extended beyond the external ring but not into the scrotum.
Size III: Hernias in which the sac extended into the scrotum.

TABLE 9.—*Unilateral and Bilateral Hernias* *

(A)

	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Unilateral, right	149	24.7	113	15	13.3
Unilateral, left	98	16.2	78	12	15.4
Total unilateral	248	40.9	191	27	14.1
Total bilateral	357	59.1	267	41	15.4
Total right	328	54.2	251	40	15.9
Total left	277	45.8	207	28	13.5
Totals	605	100.0	458	68	14.8

(B)

Bilateral hernias repaired separately: recurrences, 15.2%
Bilateral hernias repaired at one sitting: recurrences, 15.9%

(C)

Unilateral hernias: recurrences, right, 55.5% of total; left, 44.5% of total
Bilateral hernias: recurrences, right, 61.0% of total; left, 39.0% of total

* Each hernia was counted individually. Each direct inguinal hernia was considered one of two bilateral inguinal hernias when there was or had been an inguinal hernia of any type on the opposite side.

than twice that found when the sac was limited to the inguinal canal, 17.4 and 20.9 per cent for the former and 8.2 per cent for the latter.

The only death following repair of a direct inguinal hernia occurred in the group in which the sac extended into the scrotum, giving a mortality rate for that group of 2.3 per cent. This death followed operative reduction and repair of a strangulated hernia.

Unilateral and Bilateral Hernias.—The incidence of bilateral hernias among direct inguinal hernias was nearly twice that found among incom-

plete indirect inguinal hernias, 59.1 per cent as compared to 32.7 per cent. As with the other types of inguinal hernias, each direct hernia was considered one of two bilateral hernias when there was at the same time, had been previously or later developed an inguinal hernia of any type on the opposite side.

The slightly increased incidence on the right side was essentially the same with these two types of hernia. The recurrence rate after repairs of direct inguinal hernias was slightly greater for the right side than for the left.

As contrasted to the 50 per cent increase in the incidence of repairs of bilateral hernias over that of repair of unilateral hernias found among the incomplete indirect inguinal hernias, there was no apparent influence on the recurrence rate whether the direct hernias were unilateral or bilateral, or when they were bilateral, whether the two repairs were

TABLE 10.—*Incarceration and Strangulation*

Incarcerated or Strangulated	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither	579	95.7	441	65	14.5	0 in 301 operations	0.0
Incarcerated*	19	3.1	10	2	20.0	1 in 12 operations†	8.3
Strangulated*	10	1.6	9	2	22.2	1 in 3 operations†	33.3
Totals	606	100.0	458	68	14.8	1 in 312 operations	0.32

* In 3 patients strangulation developed in old incarcerated hernias. One showed no recurrence; 1 had a recurrence; 1 died.

† The single death was due to a volvulus which developed after operative reduction and repair of a hernia in which strangulation developed in an old incarcerated hernia.

done at one operation or two. However, in the majority of instances those bilateral direct hernias presenting major difficulties in the performance of a satisfactory repair were repaired by two operations.

Incarceration and Strangulation.—The incidence of incarceration in these direct inguinal hernias, 3.1 per cent, was only one half that for incomplete indirect inguinal hernia, 6 per cent. This is probably due to the fact that direct hernias, on the average, have a larger opening into the abdomen. However, the incidence of strangulation was the same for the two types of hernia, 1.6 and 1.8 per cent respectively.

After repair of direct inguinal hernias in the presence of incarceration or strangulation, the incidence of recurrence was approximately 50 per cent greater than when neither of these complications was present, 20 and 22.2 per cent respectively as contrasted to 14.5 per cent. The proportionate increases averaged somewhat less than the same figures for incomplete indirect inguinal hernias.

The only death followed repair of a strangulated hernia. This strangulation had developed, however, in a hernia which was incarcerated before the onset of strangulation.

RESULTS ACCORDING TO TYPES OF OPERATIONS

Only major differences in technic have been taken into account in classification of these operations. Five types of repair were considered to differentiate the major variations as to operative technic. These in

TABLE 11.—*Type of Repair*

Type of Repair *	Total Followed	Per Cent Recurrences	Per Cent † Infections	Per Cent † Infections Showing Recurrences	Recurrences	
					Indirect	Direct
1	19	5.3	5.3	0.0	0.0	100.0
1A	1	0.0	0.0	...	...	.....
2	94	11.7	4.2	0.0	0.0	100.0
2A	71	11.3	1.5	0.0	0.0	100.0
2B	4	0.0	25.0	0.0	...	.....
3	13	7.6	5.2	0.0	0.0	100.0
4	81	16.9	4.9	25.0	15.4	84.6
4A	77	10.4	7.8	0.0	12.5	87.5
4B	1	0.0	0.0	...	....	....
5	97	25.8	5.2	25.0	12.5	87.5
All repairs excluding rectus transplants	361	11.9	...	...	...	....
All repairs without fascial sutures	304	17.1	3.8	...	...	....
Same, without rectus transplants	207	13.0	...	...	...	....
All repairs with fascial sutures	154	10.4	5.2	...	...	....
Totals	458	14.8	4.2		8.8	91.2

* Type 1: Repairs without transplantation of the cord.

Type 1A: Same as type 1, with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle.

Type 2: Repairs with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle.

Type 2A: Same as type 2, with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle.

Type 2B: Same as type 2, with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the fascia lata.

Type 3: Repairs with transplantation of the cord between the overlapped layers of the aponeurosis of the external oblique muscle.

Type 4: Repairs with transplantation of the cord external to the aponeurosis of the external oblique muscle, with or without overlapping of the aponeurosis.

Type 4A: Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle.

Type 4B: Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the fascia lata.

Type 5: Repairs in which the rectus muscle or the anterior sheath of the rectus were sutured to the inguinal ligament.

† The percentages of infections were calculated on the entire number of repairs in each group. The percentages of infected wounds showing recurrences were calculated according to the number of recurrences found among the total infected wounds in each group which were examined in the follow-up clinic for nine months or longer.

turn have been subdivided according to the suture used, whether catgut alone or a fascial suture plus catgut. No repairs with silk were included in this series. A few were done with kangaroo tendon sutures, but the results were in no way different from the average.

The different types of repair were as follows:

Type 1.—Repair with catgut sutures only, without transplantation of the cord.

Type 1A.—Same as type 1, except that the conjoined tendon was sutured to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle, after the technic of McArthur.

Type 2.—Repair with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle, after the technic of Bassini, with catgut sutures only.

Type 2A.—Same as type 2, except that the conjoined tendon was sutured to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle, after the technic of McArthur.

Type 2B.—Same as type 2, except that a fascial suture from the fascia lata was used to suture the conjoined tendon to the inguinal ligament, after the technic of Gallie.

Type 3.—Repair with transplantation of the cord between the overlapped layers of the external oblique aponeurosis, after the technic of Willy-Andrews, with catgut sutures only.

Type 4.—Repair with transplantation of the cord external to the external oblique aponeurosis, with or without overlapping of the aponeurosis, after the technic of Halsted, with catgut suture material only.

Type 4A.—Same as type 4, with a fascial suture from the aponeurosis of the external oblique muscle used to suture the conjoined tendon to the inguinal ligament, after the technic of McArthur.

Type 4B.—Same as type 4, with a fascial suture obtained from the fascia lata used to suture the conjoined tendon to the inguinal ligament, after the technic of Gallie.

Type 5.—Any of the aforementioned types of repair in which the rectus muscle or the anterior sheath of the rectus muscle was sutured to the inguinal ligament. This included no repairs in which fascial sutures were utilized.

In a consideration of the results obtained with the various types of repair, one must bear in mind that the majority of those hernias which presented particular difficulties as to obtaining a permanent cure fell in the classifications in which a fascial suture was used or transplantation of the rectus muscle or sheath was done. Also, the majority of those hernias which presented the greatest probability of permanent cure were repaired with a technic in which the cord was not transplanted.

Suture of the rectus muscle or of the anterior sheath of the rectus muscle to the inguinal ligament in the repair of direct inguinal hernias proved to give disappointing results, as had also been observed in repairs of incomplete indirect inguinal hernias. The use of this technic was followed by recurrence in one fourth of the repairs. Its use

has been discontinued. The recurrence rate of 11.9 per cent, which is the average for all repairs excluding those in which transplantation of the rectus muscle was done, represents a much fairer expectation of recurrence in the repair of direct inguinal hernias as done at present than does the figure 14.8 per cent, which was the recurrence rate for the entire group.

Again, as with repairs of incomplete indirect inguinal hernias, transplantation of the cord superficial to the aponeurosis of the external oblique muscle without use of a fascial suture gave the highest recurrence rate, 16.9 per cent, except in that group in which transplantation of the rectus muscle was done.

Also, the average recurrence rate when fascial sutures were used, 10.4 per cent, was less than that noted when they were not used, 17.1 per cent. Even after elimination of those repairs in which transplantation of the rectus muscle or sheath was done, the recurrence rate, 13 per cent, was greater than when fascial sutures were used, 10.4 per cent. As has been stated previously, the latter group contained a much greater proportion of hernias in which attainment of a satisfactory repair presented the greater difficulties. Consequently, the expectancy recurrence in the group repaired with fascial sutures would have been correspondingly larger had the two groups of hernias been repaired by the same method.

The incidence of wound infection, 4.2 per cent, was one third more than in incomplete indirect inguinal repairs. This increase was associated with practically all types of operation but appeared to have little influence on the recurrence rates.

POSTOPERATIVE COMPLICATIONS

The incidence of postoperative complications, 21.1 per cent, was double that following repair of incomplete indirect inguinal hernias, 10.4 per cent. An increase would be normally expected, as repair of direct inguinal hernias requires a more extensive operation on the average. This increase was also present with respiratory complications, the figures being 13.3 and 7.3 per cent respectively. The incidences of circulatory complications were essentially the same, 3 per cent for direct inguinal hernias and 2.8 per cent for incomplete indirect inguinal hernias. The former type of complication gave an increase in the recurrence rate to 21 per cent, while the latter gave essentially the average, the figure being 14.3 per cent.

Wound infection developed after 4.2 per cent of the repairs as compared to 3.5 per cent of repairs of incomplete indirect inguinal hernias. Recurrences were found later with 16.3 per cent of the infected wounds, as compared to 14.8 per cent for the entire group of repairs of direct inguinal hernias.

OPERATIVE MORTALITY

Only 1 death followed the 312 successive repairs of direct inguinal hernias performed in the ten year period from 1926 to 1935. The mortality figure was 0.32 per cent. The patient who died was 75 years of age. Strangulation had developed in an old incarcerated hernia, the strangulation having been present two days before the patient's admis-

TABLE 12.—*Postoperative Complications.*

Complication	Total Operations	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Acute bronchitis	39	7.9	19.0	36	9	25.0	5.1	0	0.0
2. Wound infection	24	4.2	20.1	19	3	16.3	...	0	0.0
3. Bronchopneumonia	16	2.8	32.0	11	1	9.1	0.0	0	0.0
4. Lobar pneumonia	9	1.6	46.1	8	1	12.5	22.2	0	0.0
5. Hematomata	7	1.2	15.0	7	1	14.3	0.0	0	0.0
6. Cystitis	4	0.7	21.0	3	2	66.7	0.0	0	0.0
7. Deep phlebitis	4	0.7	31.0	3	0	0.0	0.0	0	0.0
8. Pulmonary embolus	4	0.7	30.8	3	1	33.3	0.0	0	0.0
9. Acute tonsillitis	3	0.5	20.0	1	0	0.0	0.0	0	0.0
10. Hemorrhage—patient reoperated on	2	0.3	22.5	1	0	0.0	50.0	0	0.0
11. Pulmonary atelectasis	2	0.3	16.0	2	0	0.0	0.0	0	0.0
A. Atelectasis (right lung)	1	0.2	16.0	1	0	0.0	0.0	0	0.0
B. Atelectasis (left lung)	1	0.2	16.0	1	0	0.0	0.0	0	0.0
12. Pleurisy with effusion	1	0.2	28.0	0	..	...	0.0	0	0.0
13. Empyema	1	0.2	108.0	1	1	100.0	0.0	0	0.0
14. Urethritis	1	0.2	14.0	1	0	0.0	0.0	0	0.0
15. Uremia	1	0.2	39.0	1	0	0.0	100.0	0	0.0
16. Volvulus	1	0.2	7.0	0	..	...	0.0	1	100.0
Totals	119	21.1		97	19	19.6	5.0*	1	0.84

* Excluding those patients whose only complication was wound infection.

TABLE 13.—*Postoperative Respiratory Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Acute bronchitis	39	7.1	19.0	36	9	25.0	5.1	0	0.0
2. Bronchopneumonia	16	2.8	32.0	11	1	9.1	0.0	0	0.0
3. Lobar pneumonia	9	1.6	46.1	8	1	12.5	22.2	0	0.0
4. Pulmonary embolus	4	0.7	30.8	3	1	33.3	0.0	0	0.0
5. Acute tonsillitis	3	0.5	20.0	1	0	0.0	0.0	0	0.0
6. Pulmonary atelectasis	2	0.3	16.0	2	0	0.0	0.0	0	0.0
A. Atelectasis (right lung)	1	0.2	16.0	1	0	0.0	0.0	0	0.0
B. Atelectasis (left lung)	1	0.2	16.0	1	0	0.0	0.0	0	0.0
7. Pleurisy with effusion	1	0.2	28.0	0	..	...	0.0	0	0.0
8. Empyema	1	0.2	103.0	1	0	0.0	0.0	0	0.0
Totals	75	13.3		62	13	21.0	5.3	0	0.0

sion to the hospital. Resection of the strangulated loop of ileum was not considered necessary. Death occurred on the seventh postoperative day, immediately following an operation for volvulus.

FOLLOW-UP DATA

Of the 605 direct inguinal hernias studied, 40 were not repaired. Of the 565 patients with hernias repaired, 41 did not return for follow-up observation. Sixty-six were examined over periods of less than nine months without discovery of a recurrence. Among 524 repairs

TABLE 14.—*Circulatory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Hematomas.....	7	1.2	15.0	7	1	14.3	0.0	0	0.0
2. Deep phlebitis.....	4	0.7	31.0	3	0	0.0	0.0	0	0.0
3. Pulmonary embolus..	4	0.7	30.8	3	1	33.3	0.0	0	0.0
4. Hemorrhage—patient reoperated on.....	2	0.3	22.5	1	0	0.0	50.0	0	0.0
Totals.....	17	3.0		14	2	14.8	6.5	0	0.0

TABLE 15.—*Deaths (1926-1935)*

Operative Deaths*	Patient's Age	Hernia Strangulated	Duration of Strangulation	Resection Required	Time of Death	Cause of Death
1	75	Yes	2 days	No	7 days after operation	Volvulus

* One death in 312 operations, giving a mortality rate of 0.32 per cent.

examined at some time after the patient left the hospital (average time of follow-up, twenty-nine and five-tenths months), 68 recurrences were discovered, giving a recurrence rate of 12 per cent.

Among the 458 repairs followed for nine months or longer or until a recurrence was discovered, the recurrence rate was 14.8 per cent. The average time of follow-up for this group (i.e., those followed for nine months or longer) was thirty-three and two-tenths months. The average time at which the recurrences were discovered was twenty-six months after the operation.

The number of follow-ups ending in successive periods with recurrences discovered in the corresponding periods are given in table 16 (B). Sixty-nine per cent of the total number of recurrences were found within

two years after the repairs were done. Nearly one third of the recurrences were discovered two years or more postoperatively, and one fourth, three or more years after the repairs were done.

The proportion of direct recurrences, 91.2 per cent, was greater than that which followed primary repair of incomplete indirect inguinal hernias, 60 per cent, although the former figure was the same as that which followed repair of indirect inguinal recurrences.

TABLE 16.—*Follow-up Data.*

A

Total number of hernias studied	605
Total with no operation	40
Total operations	565
Total operative deaths	1
Total with no follow-up examination	41
Total with follow-up under 9 months—no recurrences	66
Total with follow-up 9 months and over (including recurrences)	458
Average follow-up time for all cases followed 9 months and over	33.2 months
Total recurrences	68
Average postoperative time recurrences were first noted	26.0 months
Percentage of recurrences with follow-up of 9 months and over	14.8%
Total number of operations examined postoperatively	524
Average follow-up time (all followed cases)	29.5 months
Total recurrences	68
Percentage of recurrences (all followed cases)	12.9%
Recurrences: indirect, 8.8%; direct, 91.2%	

B

Length of Follow-Up*	Total Operations Followed	Per Cent of All Followed Operations	Total Recurrences Discovered	Percentage of Total Recurrences	Recurrence Percentage for Group
Under 9 months	86	16.4	20	29.4	23.2
9 months to 1 year	68	13.0	10	14.7	17.2
Under 1 year	154	29.4	30	44.1	19.5
1 to 2 years	145	27.7	17	25.0	11.7
2 to 3 years†	126	24.0	4	5.9	3.2
3 to 5 years‡	29	5.5	5	7.4	18.5
5 to 10 years	34	6.5	8	11.8	15.2
10 to 15 years	30	5.7	4	5.9	13.3
15 to 22 years	6	1.1	0	0.0	0.0
Totals	524	100.0	68	100.0	12.0

* Cases included in that group in which the follow-up period was ended either by failure to return again for examination or by discovery of a recurrence.
† Nearly one third of the recurrences were discovered 2 years or longer after the operation.
‡ One fourth of the recurrences were discovered 3 or more years after the operation.

COMMENT

A study has been made of 605 direct inguinal hernias, of which 565 were repaired.

In a consideration of the recurrence rates given in the various tables for repairs of inguinal hernias, it must be borne in mind that division of these hernias into indirect and direct as a clearcut grouping is not possible.

All hernias which were indirect but showed a direct weakness or bulge were classified among the indirect inguinal hernias. All hernias

in which there was both indirect and direct herniation in the same inguinal canal were classified as indirect or direct, depending on which of the two sacs was the larger. This routine was carried out whether the sac was of the saddle bag variety or there were two internal openings placed some distance apart. All hernias in the semilunar line were considered as direct inguinal hernias, without differentiation.

As a result of this method of classifying the hernias, a considerable group fell within the classification of indirect hernias in which the direct weakness, bulge or smaller hernia was undoubtedly of much greater significance in the question of the probability of recurrence than was the larger, indirect sac which had caused the patient's decision to have the repair performed. Classifying the simpler direct types with these direct hernias would have lowered the incidence of recurrence for repair of direct hernias.

The average age at which these hernias were first noted was ten years later in life than the corresponding figure for incomplete indirect inguinal hernias. The average age at the time of admission or repair was nine years later in life than was the case with incomplete indirect inguinal hernias. The average duration of these hernias (from the time when they were first noted to the time of admission to the hospital or operation) was one year less than that of incomplete indirect inguinal hernias. The recurrence rate for direct hernias in males was double that for incomplete indirect inguinal hernias (15.2 and 7.5 per cent respectively), while for females these figures were nearly the same, 5.5 and 4.9 per cent respectively.

A history of definite trauma as the etiologic factor in the development of the direct inguinal hernias was given in a slightly greater proportion of cases than was the case with incomplete indirect inguinal hernias.

Fewer of the sacs of direct inguinal hernias extended into the scrotum than was found to be the case with incomplete indirect inguinal hernias. Correspondingly, a greater proportion extended only beyond the external ring or were limited to the inguinal canal. Repairs of direct inguinal hernias with the longer sacs were followed by greater increases in the percentages of recurrence than was found to be the case when the sac was limited to the inguinal canal.

A smaller percentage of direct hernias were incarcerated than was the case with indirect hernias, although the percentages of strangulated hernias were practically the same in the two instances.

Repair of direct inguinal hernias by suture of the rectus muscle or the anterior sheath of the rectus muscle to the inguinal ligament was found to be an unsatisfactory procedure. Even after elimination of the aforementioned type of repair from all operations in which catgut sutures only were used, a greater incidence of recurrence was found than that

which followed the use of fascial sutures. This was true notwithstanding the fact that a greater percentage of the more difficult repairs were included in the latter group. The conclusion may be drawn from this that use of a fascial suture in the repair of direct inguinal hernias is a worth while procedure.

Postoperative complications developed after twice as great a percentage of repairs of direct as of incomplete indirect inguinal hernias.

The incidence of direct and that of incomplete indirect inguinal hernias as to location (right or left) was the same.

Nearly twice as great a proportion of direct inguinal hernias as of incomplete indirect inguinal hernias were bilateral (i. e., were associated with an inguinal hernia of some type on the opposite side).

The proportion of direct recurrences following repair of direct inguinal hernias was the same as that following repair of indirect inguinal recurrences and 50 per cent greater than that following repairs of incomplete indirect inguinal hernias.

REPAIR OF DIRECT INGUINAL HERNIAS

As is the case with all other types of hernia, these repairs deserve careful, clean dissection; sutures should be tied only tight enough to give approximation of tissues, and perfect hemostasis must be obtained, the bleeding vessels being clamped and tied without inclusion of adjacent tissues. Approximation of the cut edges of the external oblique aponeurosis will be facilitated by placing the first suture at the medial end of the incision to form the external ring and drawing the cord downward, so that it lies in a straight line in the inguinal canal before this first suture is tied. If silk suture material is to be used, and I feel that it should be, no continuous sutures should be used. In closing the wound, particular care should be exercised to leave no dead spaces. This, together with careful hemostasis, will prevent collection of serum in the closed incision.

The figures in this study would indicate that all, or practically all, direct hernias should be repaired by proper and careful use of a fascial suture. In my opinion, this should be done with a silk technic throughout. Whether part or all of the repairs should be done with a silk technic without fascial sutures, only a longer experience and a larger follow-up series for comparison than is now available at St. Luke's Hospital will determine.

It is my opinion that conversion of the direct sac into an indirect one in dissection of these hernias is a distinct improvement over isolation of the sac through the transversalis fascia at the point where it extends into the inguinal canal.

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USE OF SERIAL DILUTIONS IN DETERMINATION OF PROTHROMBIN BY THE ONE STAGE TECHNIC

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Recent advances in the study of blood coagulation have been stimulated by the discovery of vitamin K and its relation to prothrombin. While there is considerable variance of opinion as to the nature of blood coagulation, it can be assumed that at least five factors are necessary before this phenomenon occurs. These include ionizable calcium, thromboplastin, prothrombin, thrombin and fibrinogen. It is generally agreed that these substances act in the following manner, as was suggested by Howell [1] in 1914.

Based on this theory of coagulation, several methods for the measurement of prothrombin have been devised. Of these, the two stage method of Warner, Brinkhous and Smith [2] and the one stage method of Quick [3] have been more frequently employed than the others.

The two stage technic of Warner, Brinkhous and Smith is carried out as follows: Oxalated plasma is defibrinated by the addition of purified thrombin.[2] This defibrinated plasma is then incubated for thirty minutes to allow any residual thrombin to be inactivated by antithrombin. This plasma is then diluted serially and incubated with calcium chloride, thromboplastin and acacia, after which fibrinogen is added and the clotting time is recorded. The results are then calculated in terms of unitary prothrombin. By this method the clotting time is considered as the time necessary for fibrinogen to be converted into fibrin by thrombin.

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This work has been aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Howell, W. H.: Theories of Blood Coagulation, Physiol. Rev. **15**:435-470, 1935.

(*a*) Thromboplastin + prothrombin + $Ca^{++} \rightarrow$ thrombin

(*b*) Thrombin + fibrinogen $\rightarrow$ fibrin

2. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: Quantitative Study of Blood Clotting, Am. J. Physiol. **114**:667-675, 1936.

3. Quick, A. J.; Stanley-Brown, M., and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, Am. J. M. Sc. **190**:501, 1935.

The one stage method developed by Quick is a measurement of the time necessary for prothrombin to be converted into thrombin and for the subsequent conversion of fibrinogen into fibrin by this thrombin. The technic itself is concerned with the addition of thromboplastin and calcium chloride to oxalated plasma, after which the clotting time is measured. The results are expressed in terms of a standard time of twelve to fifteen seconds.

By and large, the clinical results of these two methods have compared favorably. Theoretically, any difference between the two rests on the consideration of whether prothrombin is converted into thrombin instantaneously, as has been maintained by Quick, or whether this process is gradual and time consuming, as has been held by Smith. In practice the two stage method is more difficult to perform, and consequently the one stage method is more easily adapted to extensive clinical use. The thromboplastic substances employed by these workers are derived from different tissues; cephalin, as used by Quick,[3] is obtained from the rabbit brain, while the aqueous soluble tissue extract used by Smith[2] is obtained from beef lung. Smith and his associates[4] suggested that the tissue extract is more advantageous because of its water solubility, while cephalin as used by Quick represents an emulsion. We have found the lung extract very serviceable, and it remains potent for many weeks. The activity of crude thromboplastic substances may vary slightly from day to day, thus producing minor changes in the clotting times of both normal and abnormal plasmas. Consequently, it is more desirable to compare the clotting time of abnormal plasma with that of normal plasma in a test run at the same time than to compare the abnormal clotting time with a fixed standard coagulation time.

Experimental data are presented here concerning the determination of prothrombin by a modified one stage technic. All determinations were carried out at 37 C., with lung extract[2] as the thromboplastic substance and with a test of normal human plasma run with each group of determinations. Clotting times were determined on ten serial dilutions of each plasma, with concentrations ranging from 50 per cent to 5 per cent of the original undiluted plasma. A final standard volume was maintained with oxalated saline solution[2] in each sample. All volumetric measurements were made with micropipets.

In chart 1 is shown the clotting time of oxalated plasmas when serially diluted with oxalated saline solution, with addition of thromboplastin and calcium chloride. Curve 1 is representative of normal human plasma, while curves 2 and 3 represent prothrombin-deficient plasmas. It will be seen from this chart that it was necessary to dilute

4. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Lung Extract and Blood Coagulation, Am. J. Physiol. **107**:63-69, 1934.

the normal plasma to less than 35 per cent of its original concentration before any change in clotting time occurred. It is apparent from curves 2 and 3 that a prolonged clotting time may be evident in the 50 per cent plasma concentration or that it may appear at any point down to the 35 per cent level, according to the degree of prothrombin deficiency present. We have not observed an abnormal plasma which did not exhibit a prolonged clotting time before the 35 per cent plasma concentration was reached, although the degree of abnormality was sometimes so slight as to be difficult to read. In such cases the more dilute plasmas magnify any differences, so that they become more readily

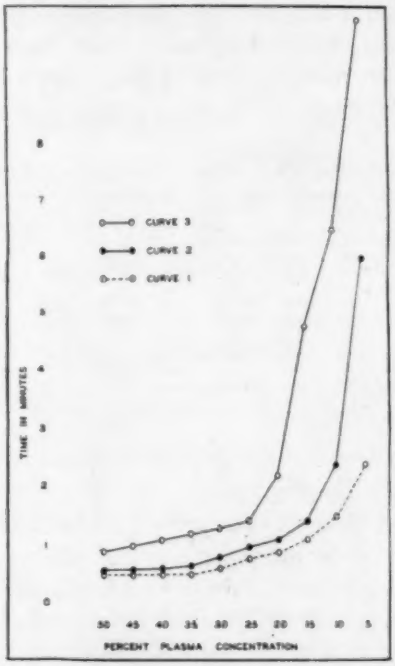

Chart 1.—Relation between coagulation time and concentration of normal and of prothrombin-deficient plasmas.

apparent. The results so obtained then can be compared with the clotting curve of the normal control. The early, straight line portion of the curve for normal plasma is probably representative of an excess of plasma prothrombin which this technic is not sufficiently sensitive to record.

When fibrinogen [2] was added in increasing volumes, thus replacing the oxalated saline solution used in maintaining the standard volumes of the serial dilutions, no significant deviation from the control clotting

time was observed until the 15 per cent plasma concentration was reached (chart 2). Since a small amount of prothrombin could still be demonstrated in the fibrinogen used, it appears that most, if not all, of this slight reduction in the clotting time could be accounted for on the basis of the prothrombin contained in this fibrinogen. From this curve it is highly suggestive that the dilution of fibrinogen which accompanies the dilution of prothrombin in the technic used here is not a factor in the alteration of clotting time.

The advantages of serial dilution in the one stage technic are readily apparent in cases in which the prothrombin response to vitamin K is minimal or sluggish. The case of nontropical sprue mentioned in the table illustrates such a sluggish response; sixteen days of oral administration of 2-methyl-1, 4-naphthoquinone were necessary to restore the prothrombin time to normal. The clotting times presented here have been interpreted in terms of the coagulation time of a single normal

Slow Return to Normal of the Clotting Time in a Case of Nontropical Sprue

No. of Days of Naphthoquinone Therapy	Per Cent of Plasma Concentration									
	50 Min.	45 Min.	40 Min.	35 Min.	30 Min.	25 Min.	20 Min.	15 Min.	10 Min.	5 Min.
1	0.83	0.90	1.01	1.10	1.19	1.30	2.10	4.70	6.40	10.20
5	0.80	0.89	0.97	1.08	1.30	1.42	1.60	1.82	3.25	7.65
7	0.65	0.65	0.65	0.76	1.00	1.24	1.30	1.60	2.80	6.50
11	0.52	0.55	0.57	0.61	0.71	0.85	0.90	1.14	1.64	4.42
16	0.46	0.46	0.46	0.46	0.57	0.72	0.80	0.95	1.46	3.40
Normal control	0.46	0.46	0.46	0.46	0.57	0.72	0.78	0.97	1.43	3.53

control. Thus it is seen that the more dilute plasmas more readily reflect minor changes in the clotting time.

In the course of these studies several patients showed prolongation of the clotting time of the more concentrated plasmas in the coagulation curve, while at the same time in the more dilute plasmas of these patients the clotting times approximated those of the normal control. An example of this phenomenon is shown graphically in chart 3. These data were obtained from the plasma of a patient during the course of serum sickness which appeared ten days after antipneumococcic rabbit serum had been given. At the height of the illness many spontaneous ecchymotic areas appeared in the skin and subcutaneous tissues. Whether this phenomenon represented release into the blood stream of an inhibitory, or heparin-like, substance is, of course, not known. It is interesting, however, that in the experimental animal Jaques and Waters [5] have recently

5. Jaques, L. B., and Waters, E. T.: The Isolation of Crystalline Heparin from the Blood of Dogs in Anaphylactic Shock, read at the meeting of the American Physiological Society, New Orleans, March 13-16, 1940; Proc. Am. Physiol. Soc., 1940, p. 93.

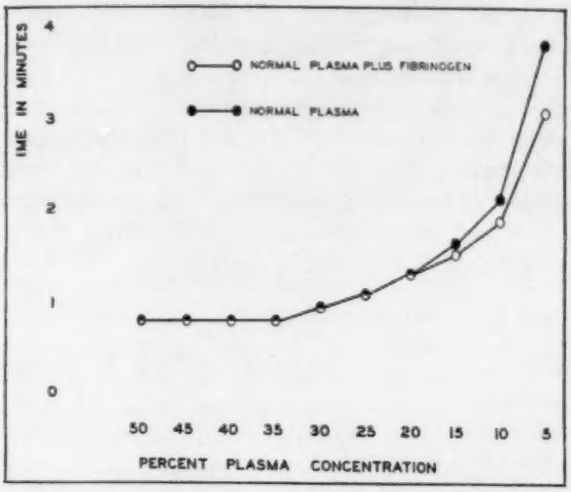

Chart 2.—Graph showing that the dilution of fibrinogen accompanying the serial dilution of plasmas as employed in this study does not materially alter the coagulation curve.

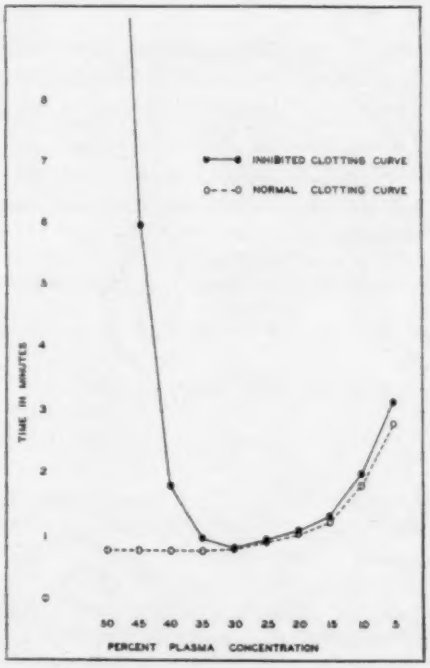

Chart 3.—Inhibition of coagulation in a patient with serum sickness (see text).

reported the presence of crystalline heparin in the circulating blood after anaphylactic shock. Consequently, the data presented here are suggestive that a similar condition may occur in the human patient. The effect of an inhibitory substance was also demonstrated to a lesser degree in 4 patients during early postoperative periods. In none of these patients could this effect be demonstrated for more than forty-eight hours after its initial appearance. In vitro studies (not reported here) concerned with the addition of heparin to normal human plasma indicate that this anticoagulant is capable of altering the coagulation curve so that it has the same form as that shown in chart 3.

SUMMARY

A modification of the one stage technic for prothrombin determination is presented.

Variations of concentrations of fibrinogen in the plasma and its effect on prothrombin time are noted.

The value of serial dilutions of plasma in cases in which the response to vitamin K is sluggish is pointed out.

An inhibitory substance has been demonstrated in a patient suffering from serum sickness. The importance of employing the serial dilution technic for detection of this substance is discussed.

NOTE.—Since submitting this paper for publication we have become aware of a report by Kark and Lozner [6] in which they present a different type of dilution technic for determination of prothrombin by the one stage method. These workers have expressed the belief that their procedure will enable one to detect changes in prothrombin concentration which ordinarily would not be recognized, and our experience would support their conclusions.

6. Kark, R., and Lozner, E. L.: Nutritional Deficiency of Vitamin K in Man, Lancet **2**:1162, 1939.

LOCALIZATION OF STAPHYLOCOCCI IN AREAS OF INFLAMMATION PRODUCED BY XYLENE

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The phrase "locus minoris resistentiae" is hoary with years, and the initiation of local infective processes by injury unaccompanied with direct infection is a widely recognized fact.[1] Streptococci, when given intravenously, have been observed to localize in abscesses produced by subcutaneous injection of silver nitrate.[2] Benians [3] found that Bacillus typhosus, when injected intravenously in rabbits, localized in areas of skin where agar, mucin and starch had previously been injected. Tubercle bacilli, when present in the blood stream, tend to localize in areas of necrosis and also in tissue showing an increase in vascularity.[4] As early as 1843, Cazenave [5] observed that localization of a secondary syphilitic lesion is commonly determined by some concomitant irritation or morbid condition.

Findlay,[6] in 1928, studied the problem of localization of bacteria in areas of injury. He stated:

> When bacteria are present in the blood stream, their passage through the wall of the capillaries is difficult, except at those points where there is increased permeability (and probably also increased stickiness) of the capillary endothelium. At these points organisms, therefore, tend to pass through the capillary endothelium and collect in the surrounding tissues. The localization of organisms in injured tissues is thus dependent on a change in permeability of the capillary endothelium. The subsequent development of a lesion in the tissues is conditioned by

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Aided by grants from the John and Mary R. Markle Foundation and from the University of Tennessee.

1. Burrows, H.: Localization of Disease, New York, William Wood & Company, 1932.

2. Sager, W. W., and Nickel, A. C.: Localization of Bacteria in Tissues of Lowered Resistance, Arch. Surg. **19**:1086 (Dec., pt. 1) 1929.

3. Benians, T. H. C.: Septicemia: The Selective Deposition of Colon Typhoid Group of Bacteria in Fixation Abscesses, Brit. J. Exper. Path. **2**:276, 1921.

4. Kettle, E. H.: Demonstration by Fixation Abscess of Influence of Silica in Determining B. Tuberculosis Infections, Brit. J. Exper. Path. **5**:158, 1924.

5. Cazenave, P. L. A., and Schedel, H. E.: Manual of Diseases of the Skin, translated by T. H. Burgess, New York, Samuel S. Wood & William Wood, 1852.

6. Findlay, G. M.: Histamine and Infection, J. Path. & Bact. **31**:633, 1928.

the number and virulence of the organisms which have passed through the permeable capillary wall and on the state of the surrounding tissue cells.

The localization and concentration of trypan blue, india ink, staphylococcus antitoxin and the virus of vaccinia in areas of inflammation produced by local application of xylene have recently been studied.[7] It was found that each of the aforementioned substances localized and concentrated in areas of inflammation only during a specific interval after application of the irritant. Furthermore, the localization and concentration of trypan blue, india ink, staphylococcus antitoxin and the virus of vaccinia were not determined by either the presence or the absence of either edema or hyperemia.

In the present experiment an attempt has been made to study the mechanism by which staphylococci localize in areas of inflammation.

MATERIAL AND METHODS

The staphylococci were grown on the surface of agar in large flat bottles for twenty-four to forty-eight hours. The bacteria were then carefully scraped away, washed three times in large volumes of saline solution and suspended in physiologic solution of sodium chloride. The suspension of staphylococci was heavy enough to appear milky white. Ten cubic centimeters of this suspension was injected into the marginal vein of the ear.

Both sides and the abdomen of the rabbit were carefully shaved twenty-four hours or longer before the experiment was begun. Xylene was gently applied on a cotton swab to local areas of skin approximately 2 by 2 cm. at varying intervals before the bacteria were given. In one part of this experiment xylene was applied to several areas of skin at the same time, immediately before the staphylococci were injected.

The rabbits either died or were killed at specific intervals after injection of the bacteria. Each area of skin treated with xylene was removed and divided into two portions, one of which was placed immediately into a 10 per cent concentration of solution of formaldehyde U. S. P., and the second of which was put into the incubator (37.5 C.) for two to six hours, after which time it was removed and placed in a similar concentration of formaldehyde.

Areas of skin from the rabbits in which the xylene was applied to several areas at the same time were excised at intervals varying from forty minutes to six hours. The tissue was divided; one half was placed immediately into the solution of formaldehyde, and the second half was put into the incubator for six hours before it was put into the same preservative.

Sections of the skin were prepared in paraffin. They were stained routinely with hematoxylin and eosin. Select sections were stained by Giemsa's method to demonstrate the staphylococci.

RESULTS

Xylene was applied to the skin of 6 rabbits at the following intervals before the saline suspension of staphylococci was given: area 1, twenty-four hours; area 2, five hours, and area 3, immediately. The rabbits were killed one and one-half

7. Rigdon, R. H.: Capillary Permeability in Areas of Inflammation Produced by Xylene, Arch. Surg. **41**:101 (July) 1940.

hours later. Sections of the skin were removed for histologic study. Portions of the skin were kept in the incubator for only two hours in this part of the experiment.

The degree of injury produced by xylene was relatively uniform in the different areas of skin of the same rabbit and also in different rabbits. The skin usually became hyperemic within two to three minutes after application of this irritant, and frequently it was edematous within five minutes. The edema and hyperemia remained for several days, after which time the epithelium desquamated. Polymorphonuclear leukocytes apparently began to infiltrate the corium within ten to fifteen minutes after the xylene was applied. Usually, however, one and one-half hours elapsed before any significant number of leukocytes reached this tissue. Polymorphonuclear leukocytes and mononuclear cells continued to infiltrate the xylene-treated areas of skin for ten to twelve hours. At this time many of the superficial epithelial cells separated from the basement membrane, and the spaces were filled with fluid and leukocytes. The number of leukocytes apparently did not increase after the first thirty hours.[7]

A few cocci were present in the lumens of the small blood vessels in those sections of skin where xylene was applied immediately before the staphylococci were injected. Some of the bacteria were located in the cytoplasm of a few of the polymorphonuclear leukocytes present in the lumens of the blood vessels. The number of organisms was much greater in the sections that were incubated than in those placed immediately in solution of formaldehyde. Only an occasional coccus was found extravascularly. Some of the staphylococci appeared to be in the cytoplasm of the endothelial cells lining the small blood vessels in the corium.

It seemed likely that the number of bacteria could be increased and their location more easily determined by keeping the skin in the incubator for a longer time. To determine whether this was true, xylene was applied to the skin of 2 rabbits in one area eight hours before the bacteria were injected and in a second area immediately prior to inoculation. One of these rabbits died five minutes after injection of the staphylococci, and the second animal was killed after thirty minutes. One half of each of the xylene-treated areas of skin was fixed immediately in solution of formaldehyde, while the second half was put into the incubator for five hours before it was put into a similar solution.

Histologic studies showed many leukocytes in the corium in those areas of skin where xylene was applied eight hours prior to injection of the bacteria. An occasional staphylococcus was observed in the cytoplasm of some of the polymorphonuclear leukocytes present in the lumens of the blood vessels and also in some of the extravascular leukocytes. Organisms were present in the cytoplasm of the endothelial cells lining the wall of the small blood vessels in the corium immediately below the squamous epithelium in those areas of skin where xylene was applied immediately prior to injection of the staphylococci. The small blood vessels appeared to be distended with staphylococci in those sections where the xylene was applied immediately before the bacteria were injected and the tissues were put into the incubator (fig. 1 *B*). Those sections of skin to which xylene was applied eight hours before the organisms were given and which were placed in the incubator for six hours showed essentially no staphylococci; however, there were many leukocytes (fig. 1 *A*).

Comment.—The preceding experiments show that staphylococci, after an intravenous injection, localize and concentrate in areas of skin where xylene is applied only during a specific period after application of the

irritant. The bacteria remain primarily within the lumens of the small blood vessels in the corium (fig. 2). Some of the cocci appear to be within the cytoplasm of the endothelial cells lining these blood vessels. Cocci are also present in the cytoplasm of many of the leukocytes in the lumens of the blood vessels. A few leukocytes in the extravascular tissue have staphylococci within their cytoplasm.

In an attempt to study further the mechanism by which staphylococci localize in areas of inflammation, xylene was applied to three areas of skin at the same time

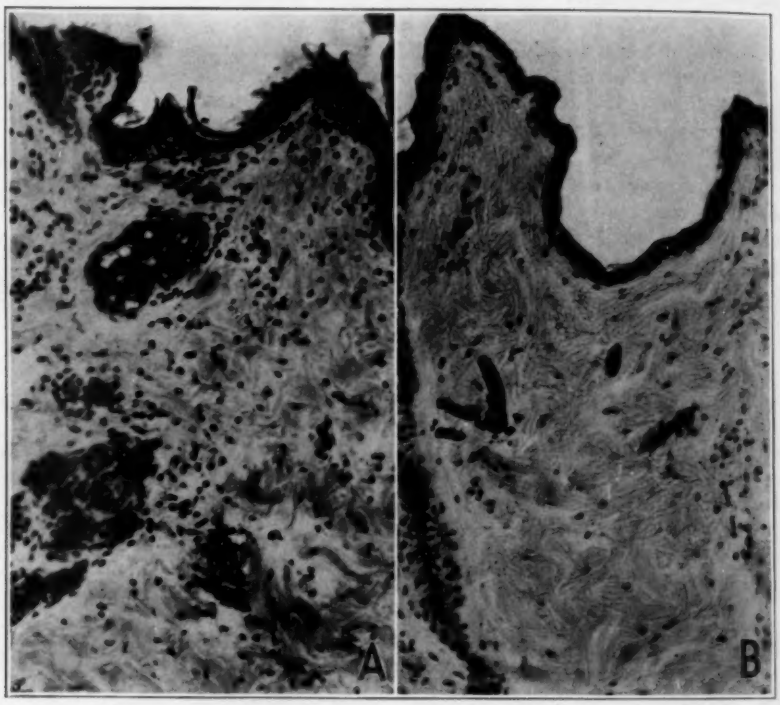

Fig. 1.—*A*, xylene was applied to the rabbit's skin seven and one-half hours before 10 cc. of a saline suspension of staphylococci was injected intravenously. This animal was killed thirty minutes later, and the xylene-treated skin was put into the incubator (37.5 C.) for five hours. It was then fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. There are a large number of polymorphonuclear leukocytes infiltrating the corium. *B*, the same rabbit as in *A* was used. Xylene was applied to this area of skin immediately before the staphylococci were injected. The tissue was treated like that shown in *A*. There are no polymorphonuclear leukocytes in the corium. The lumens of the small blood vessels are filled with staphylococci.

on each of 2 rabbits immediately before 10 cc. of a saline suspension of staphylococci was given intravenously. The rabbits were anesthetized with ether forty minutes later, and one of the xylene-treated areas of skin was removed (area 1). Two hours later a second area of the xylene-treated skin was removed (area 2).

One rabbit died ten minutes after removal of the second biopsy specimen. The third area of xylene-treated skin was removed four hours and forty minutes after injection of the staphylococci (area 3). The procedure for preserving these pieces of skin was the same as that used in the preceding experiments. The skin was kept in the incubator for six hours.

The sections of skin had no leukocytes in any of the three areas of tissue where xylene was applied, although the tissues remained in the animals sufficiently long, apparently, for these cells to reach the areas of inflammation (fig. 3, *A*, *C* and *E*).

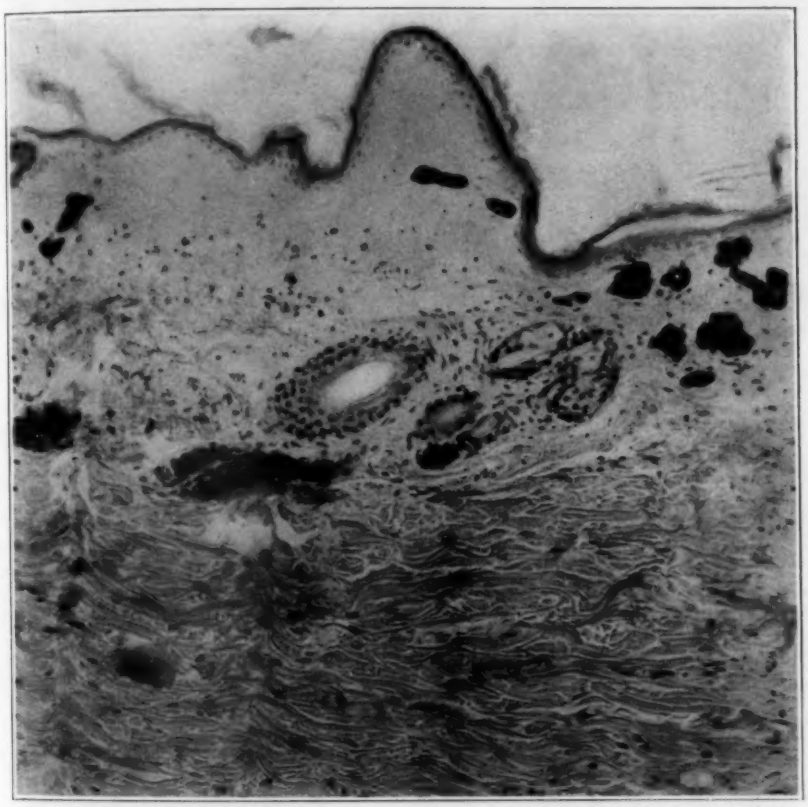

Fig. 2.—Xylene was locally applied to the skin of a rabbit immediately before 10 cc. of a saline suspension of staphylococci was given intravenously. This section was removed two hours and forty minutes later. It was placed in the incubator for six hours and then fixed in solution of formaldehyde. The lumens of the small blood vessels immediately beneath the squamous epithelium are filled with staphylococci. Vessels of similar size in other portions of this section do not have any bacteria within their lumens.

A few cocci were present in the lumens of the small blood vessels in the corium in the sections of skin removed forty minutes after intravenous injection of the bacteria. The portion of skin removed at this time and put into the incubator

showed the bacteria usually in the small blood vessels in oval or rounded masses. These collections of organisms frequently were so dense that it was impossible to see the capillary wall (fig. 3 *B*).

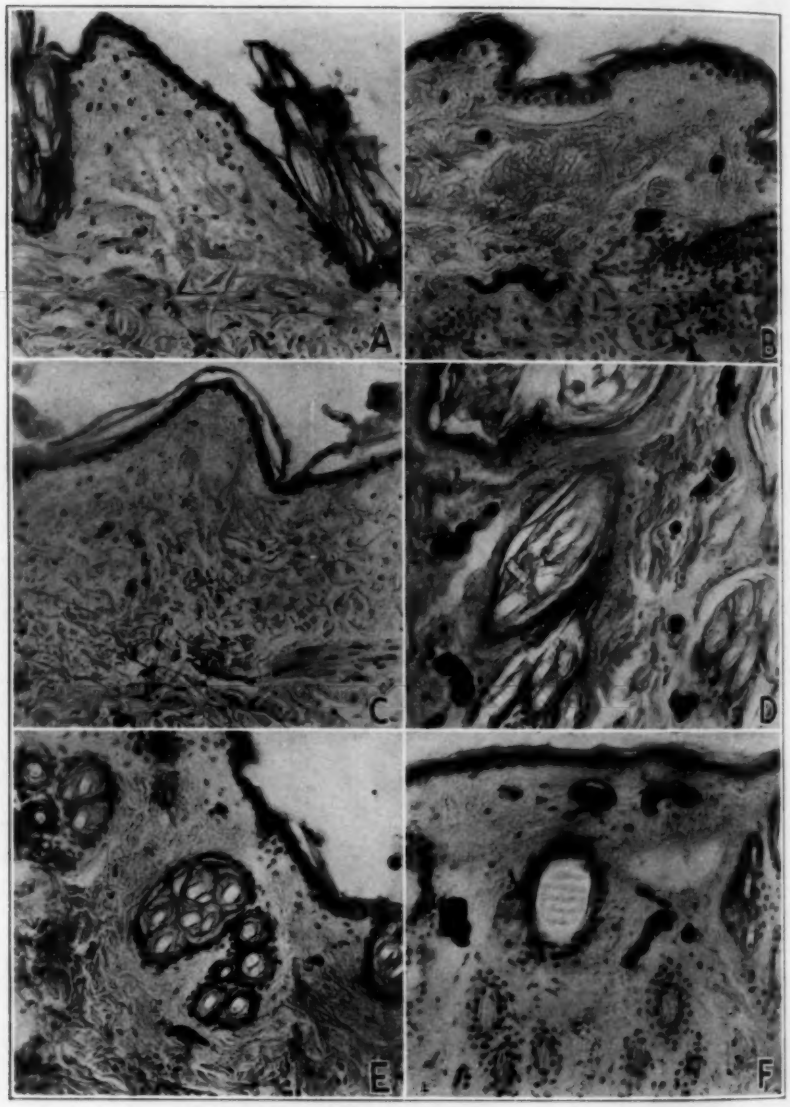

Figure 3

(See legend on opposite page)

The skin from area 2, removed two hours and forty minutes after intravenous injection of the staphylococci, showed essentially the same changes as the section removed after forty minutes (fig. 3 *C*). There was, however, a greater number

of cocci in the former. Some of the bacteria appeared to be within the cytoplasm of the endothelial cells. The corresponding half of the section of skin put into the incubator showed a greater number of cocci than were observed in the tissues removed after forty minutes and incubated for a similar period (fig. 3*D*).

The skin from area 3, removed four hours and forty minutes after the organisms were injected, showed many of the small blood vessels to be filled with staphylococci (fig. 3*E*). The bacteria were in the lumens and in the cytoplasm of the endothelial cells. A few cocci were present around the periphery of the small blood vessels. The portion of skin removed at this time and put into the incubator showed the bacteria extending out from the vessel walls into the surrounding tissues (fig. 3*F*).

GENERAL COMMENT

Staphylococci, after an intravenous injection, localize in areas of inflammation in the rabbit's skin only during a specific period after local application of xylene. The localization of these organisms in areas of inflammation is not determined by either the presence or the absence of hyperemia and edema. The time in which the cocci localize in the tissues corresponds to that observed in a recent study on the localization and concentration of trypan blue, staphylococcus antitoxin, india ink and the virus of vaccinia in areas of inflammation produced by local application of xylene to the skin of the rabbit.[7]

The staphylococci are located most frequently in the lumens and in the cytoplasm of the endothelial cells lining the walls of the small blood vessels in the corium. Only a few cocci are present in the extravascular tissues, and they are adjacent to the walls of the blood vessels. These observations suggest that staphylococci circulating in the blood may be phagocytosed by the endothelial cells lining the walls of the small blood vessels in the corium. The cocci may not reach the extravascular tissue until the endothelial cells are severely injured by the staphylococci.

Fig. 3.—The sections of skin (× 220) shown in this group are from the same rabbit. The tissues shown in *B*, *D* and *F* were put into the incubator for six hours before they were put into a 10 per cent concentration of solution of formaldehyde U. S. P. The rabbit was anesthetized with ether when each of the three sections of skin was removed. *A*: This area of skin was removed forty minutes after injection of the staphylococci. Note the absence of either staphylococci or leukocytes in the corium. *B*: Same as *A*, except that this section was put into the incubator. The lumens of many of the capillaries are filled with staphylococci. *C*: This section of skin was removed two hours and forty minutes after the staphylococci were injected. Note the absence of both leukocytes and staphylococci in the corium. *D*: Same as *C*, except that this section was put into the incubator. The lumens of the small blood vessels are filled with staphylococci. *E*: This section of skin was removed four hours and forty minutes after the staphylococci were given. The lumens of some of the small blood vessels are filled with staphylococci. There are no leukocytes in this section. *F*: Same as *D*, except that this section was put into the incubator. There are many more bacteria here than in section *E*.

It appears very unlikely that a nonmotile bacterium the size of a staphylococcus can pass extravascularly in a manner similar to that of a colloid.

There is a difference of opinion as to the mechanism by which particles localize in areas of inflammation. Such localization may result from active phagocytosis by the endothelial cells. McJunkin [8] stated that granules of india ink appear in endothelial cells as a result of a transit of these granules through the cells and not as the result of active phagocytosis. Lang [9] found that carbon particles adhere to the inner surface of the capillary endothelium only in inflamed tissues. Later they appear within the endothelial cytoplasm, and at the end of ten hours some of the particles are present in the perivascular macrophages.

The phagocytosis of bacteria and inert particles by polymorphonuclear leukocytes during circulation in the blood has been observed.[10] The finding of staphylococci in the cytoplasm of the leukocytes, both intravascular and extravascular, in this study suggests that these bacteria may be carried through the blood vessel walls in leukocytes as the latter enter the areas of inflammation. Calumette [11] discussed dissemination of tubercle bacilli through the body by leukocytes. Goodpasture [12] recently suggested that typhoid bacilli may be carried from the intestinal tract to other organs by plasma cells.

Two methods, therefore, apparently are available by which staphylococci may reach the extravascular tissues in areas of inflammation. In one the organisms either adhere or are phagocytosed by the endothelial cells. The bacterium may then reach the extravascular spaces only after the endothelial cells are severely injured. The second method consists in active phagocytosis of the bacteria in the circulating blood by the leukocytes and passage of the organism through the capillary wall within the cytoplasm of the leukocytes. The cell is then destroyed by the staphylococci. It appears to me likely that the latter method occurs more often than the former when there are only a few staphylococci in the circulating blood.

It is interesting to observe that only the small blood vessels in the corium show any staphylococci (fig. 2). Vessels of similar size in the adjacent muscle and fat do not show any cocci within their lumens.

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8. McJunkin, F. A.: Origin of the Phagocytic Mononuclear Cells of the Peripheral Blood, Am. J. Anat. **25**:27, 1919.

9. Lang, F. J.: Role of Endothelium in Production of Polyblasts (Mononuclear Wandering Cells) in Inflammation, Arch. Path. **1**:41 (Jan.) 1926.

10. Menkin, V.: Studies on Inflammation: Fixation of Bacteria and of Particulate Matter at Site of Inflammation, J. Exper. Med. **53**:647, 1931.

11. Calumette, A.: Tubercle Bacillus Infection and Tuberculosis in Man and Animal, Baltimore, Williams & Wilkins Company, 1923.

12. Goodpasture, E. W.: Concerning Pathogenesis of Typhoid Fever, Am. J. Path. **13**:175, 1937.

There is nothing in this study to indicate why staphylococci either stick or are phagocytosed by the endothelial cells during only a specific interval after local application of xylene. This same phenomenon has been observed with several substances very different from bacteria.[7]

There is apparently no satisfactory explanation at this time for the cellular changes that occur in inflammation. Menkin's[13] preparation, leukotaxine apparently will not explain this phenomenon. Several investigators have already shown that a substance may be obtained from normal tissues which when injected intradermally permits localization and concentration of an intravenous injection of trypan blue in the skin of the rabbit.[14]

The absence of polymorphonuclear leukocytes in the corium in the xylene-treated areas of skin of the 2 rabbits given intravenous injections of staphylococci at the time the irritant was applied is most interesting (fig. 3), since the skin of all the other rabbits studied to which xylene was applied several hours before the staphylococci were injected intravenously showed a large number of leukocytes in the corium. The ether used for anesthesia may have played some role; however, at this time such a factor appears insignificant.[15]

SUMMARY

Staphylococci, after intravenous injection, localize in areas of inflammation in the skin of the rabbit only during a specific period after local application of xylene. The localization of these organisms in areas of inflammation is not determined by either the presence or the absence of hyperemia and edema.

A majority of the bacteria apparently remain within the lumens and in the endothelial cells of the small blood vessels in the corium.

There appear to be two ways in which staphylococci may reach the extravascular tissues in areas of inflammation. 1. The organisms may be phagocytosed by polymorphonuclear leukocytes while they are in the lumens of blood vessels and may be carried through the vessel wall within the cytoplasm of these cells. 2. The organisms may either adhere or be phagocytosed by the endothelial cells, after which the cells are severely injured by the bacteria; this permits the latter to reach the extravascular tissue.

13. Menkin, V.: Studies on Inflammation: Mechanism of Increased Capillary Permeability, J. Exper. Med. **64**:485, 1936.

14. Rigdon, R. H.: Demonstration of a Capillary Permeability Factor in Tissue Extracts from Normal Rabbits, Arch. Surg. **41**:96 (July) 1940. Bier, O., and Planet, N.: Sur la présence d'un facteur qui augmente la permeabilité capillaire dans les extraits de peau normale, Compt. rend. Soc. de biol. **129**:65, 1938.

15. Cressman, R. D., and Rigdon, R. H.: Permeability and Inflammation in Narcotized Rabbits, Arch. Surg. **39**:586 (Oct.) 1939.

CANCER OF THE TONGUE

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Cancer of the tongue causes more deaths than any other of the malignant growths of the head and neck, and therefore it must be considered the most important tumor in that group. In comparison with other malignant growths of the upper respiratory and alimentary tracts, it is only slightly less malignant than the highly anaplastic and rapidly growing tumors of the oropharynx and nasopharynx. Excluding cancer of the lip, it is more frequent than any other single anatomic variety of cancer in this region.

The records of the Memorial Hospital for the Treatment of Cancer and Allied Diseases contain over 1,500 cases of cancer of the tongue, but since many of the older records are incomplete, we have utilized for the purpose of this report only the cases of patients admitted during the eight year period, 1927 to 1934 inclusive. This series (556 cases) comprises a consecutive group of all patients with cancer of the tongue, histologically proved, who applied to the clinic during the aforementioned period, except those in whose cases the period of observation was less than one month, owing to the patient's inability or unwillingness to return for either curative or palliative treatment. Our records show that less than 1 of 20 patients with cancer of the tongue who apply to our clinic is unable or unwilling to return. No cases have been excluded from the series because of the advanced stage of the disease.

The standards used in the makeup of this series are described in greater detail under the discussion of end results at the conclusion of

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From the Head and Neck Service, Memorial Hospital.

Read in part as the Bulkley Lecture, New York Academy of Medicine, Nov. 20, 1936.

† Former Rockefeller Fellow in Cancer Research, Memorial Hospital for the Treatment of Cancer and Allied Diseases. Dr. Munster died Dec. 21, 1939.

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this paper. In this communication, we have attempted to overcome the deficiencies common to most published reports on cancer of the tongue, which, as a rule, deal only with selected groups of tumors in early stages treated by a single method, usually surgical, and which therefore do not represent true samples of lingual cancer as this disease exists at the present time.

Definition.—The term "cancer of the tongue" as used in the present report comprises all malignant growths arising in the organ from the valleculae to the tip, including the under surface anteriorly and laterally. In some clinics, those growths which originate in the floor of the mouth anteriorly and laterally are also classified as lingual cancers. It is our opinion that such a comprehensive use of the term "cancer of the tongue" is not advisable, since the floor of the mouth is a separate anatomic structure, and growths of this region, although resembling somewhat those of the under surface of the tongue, possess individual clinical and anatomic characteristics deserving of a separate classification.

ETIOLOGY

Incidence.—Cancer of the tongue is one of the most common anatomic forms of malignant growth of the oral cavity. At the Memorial Hospital it comprises about 15 per cent of all tumors of the upper respiratory and alimentary tracts and about 25 per cent of all intraoral tumors. According to recently calculated mortality statistics furnished us by the department of health of New York city,[1] cancer of the tongue caused 1.2 per cent of all deaths from cancer. It is probable, however, that not all deaths due to cancer of the tongue are reported as such. This is particularly likely to be true of cancer of the base of the tongue, which is difficult to diagnose and is often confused with cancer of the pharynx. From our own and various other statistical data, we estimate that cancer of the tongue makes up between 2 and 3 per cent of all human cancer.

Age.—In the series herein reported, the average age of the patients was about 58 years at the time of admission to the hospital, which runs fairly close to our figures for such other forms of intraoral cancer as cancer of the cheek (59 years) and cancer of the lip (57 years). Our mean age incidence is about five years higher than that calculated by Lane-Claypon[2] from over 30 separate reports totaling over 1,000 cases. There are many reports in which the mean age incidence of cancer of the tongue is given as over 60 years, but there is general

1. Duffield, T.: Personal communication to the authors.

2. Lane-Claypon, J. E.: Report on Cancer of the Lip, Tongue and Skin, Ministry of Health, Reports on Public Health and Medical Subjects, no. 59, London, His Majesty's Stationery Office, 1930.

agreement within the range of 55 to 60 years, with a greater incidence between the ages of 60 and 64 than in any other five year period. The age of the oldest patient in the present series was 89 years, while that of the youngest was 17.

Sex.—In this series, 87 per cent of the patients were males and 13 per cent females. Other statistics of our clinic have shown that the incidence of cancer of the tongue in females is greater than that of either cancer of the lip (6 per cent) or cancer of the cheek (10 per cent).

Position of the Growth.—The topographic distribution of cancer of the tongue in our clinic varies considerably from that indicated by most of the figures reported in the literature, although there is general agree-

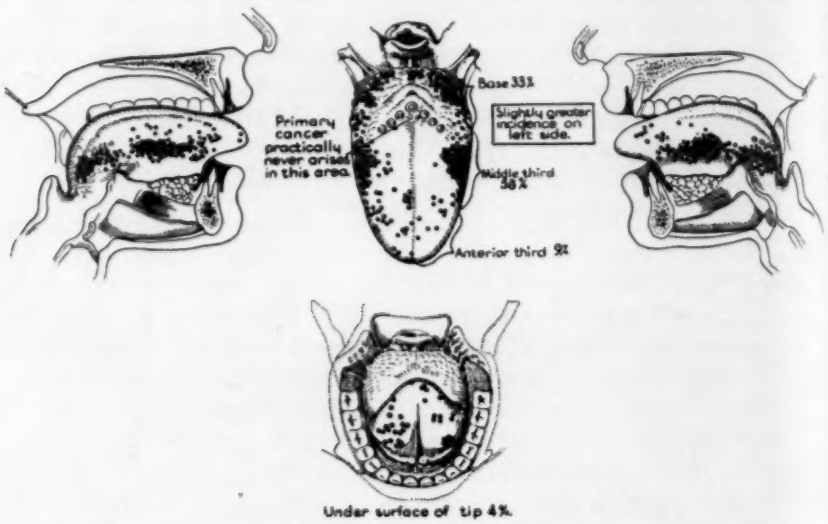
Primary cancer practically never arises in this area.
Base 33%
Slightly greater incidence on left side.
Middle third 58%
Anterior third 9%
Under surface of tip 4%

Fig. 1.—Topographic distribution in 673 cases of cancer of the tongue. The lateral border of the middle third is the most common site of origin (58 per cent), with the base of the tongue next in frequency (33 per cent). The dorsum at the line of the circumvallate papillae has never been the site of primary cancer in our experience.

ment that the most frequent site of origin is the edge of the tongue in its middle third (50 per cent in our series). The incidence in other regions is shown in figure 1. The lack of any standard classification and uniform demarcation of boundaries with regard to these other sites makes it rather difficult to compare the published figures in the various reports. This question is of little practical importance except in reference to the relative percentage of cancer of the base of the tongue. In this area, the marked discrepancies of the various reports can indicate only that cancer of the base of the tongue is not always included in the average report of lingual cancer. The diagnosis may be missed

entirely, owing to the indefinite character of the local symptoms and the moderate difficulty of physical examination, or the growth may be classified as pharyngeal rather than lingual, as MacFee [3] and Roux-Berger have pointed out. Furthermore, even though correctly diagnosed, cancer of the base of the tongue would usually be considered inoperable and for that reason would tend to be omitted entirely from strictly surgical reports.

The incidence of intraoral cancer in general seems to be greater on the left side than on the right, the ratio approaching 60:40, as has been reported repeatedly.[4] In a recent series of 252 cancers of the lip at Memorial Hospital, 57 per cent were recorded as occurring on the left, and twice as many on the left side of the upper lip as on the right side of the upper lip. The dorsum of the middle third of the tongue, especially that region just in front of the lingual V, seems to be singularly immune to the development of the initial lesion in cancer. The records of about 1,500 cases of cancer of the tongue at Memorial Hospital in no instance show the growth to have arisen in this region. This point will be discussed further under differential diagnosis.

Causative Factors.—As in other forms of cancer of the oral cavity proper, chronic irritation is an outstanding apparent etiologic factor in growths of the middle and anterior thirds of the tongue. In these areas, such precancerous changes as chronic diffuse or localized glossitis and leukoplakia most often occur. At the base of the tongue (lingual tonsils and valleculae), tissue changes as a result of chronic irritation are less definite, even in the most aggravated chronic glossitis, and are usually evidenced by an injection of the mucous membrane, an increase of lymphoid tissue and an irregularity of the mucous surface. So far as we know, leukoplakia of the tongue is never seen posterior to the lingual V. This portion of the tongue is rather well protected from several of the common forms of chronic irritation, and on first thought one might conclude that this etiologic factor is of only minor importance in cases of cancer of the base of the tongue. There is definite evidence, however, that some forms of tobacco smoking are particularly apt to cause cancer in this region.

The average wear on the teeth and the response of the soft tissues to the normal environment—eating, drinking and speaking—constitute

3. MacFee, W. F.: Concealed Cancer of the Tongue, Ann. Surg. **93**:481, 1931. Roux-Berger, J., and Jadlovker, M.: L'envahissement lymphatique dans les cancers de la base de la langue, Presse méd. **48**:249, 1940.

4. (*a*) Broders, A. C.: Squamous Cell Epithelioma of the Lip, J. A. M. A. **74**:656 (March 6) 1920. (*b*) Butlin, H. T.: Diseases of the Tongue, ed. 1, London, Cassell & Co., 1885. Butlin, H. T., and Spencer, W. G.: Diseases of the Tongue, ed. 2, London, Cassell & Co., 1900. (*c*) Regaud, C.: Radium Therapy of Cancer at the Radium Institute, Am. J. Roentgenol. **21**:1, 1929.

a definite though mild chronic irritation, but it is not with such a degree of irritant effect that this discussion is concerned. By the term "chronic irritation" as hereinafter used is meant the physiologically demonstrable abnormal effects which occur as the result of chronic trauma.

Such characteristic signs of chronic irritation in the oral cavity as leukoplakia, chronic glossitis and dental sepsis are much more prevalent in the male than in the female. The fact that cancer of the oral cavity is likewise more frequently found in the male is one of several evidences of a direct causal relationship between chronic irritation and intraoral cancer. Ahlbom's [5] investigations indicate that tobacco, syphilis and achlorhydric anemia with the Plummer-Vinson syndrome are outstanding etiologic factors in intraoral and pharyngeal cancer in Sweden.

Undoubtedly the chronicity of the irritant is more important than its nature. Most of the anatomic forms of cancer which follow chronic irritation (cancer of the skin, lip, cheek, etc.) are more common in the aged, in whom the irritant has had sufficient time to act. No one specific form of chronic irritation per se appears to be of singular importance in the etiology of cancer. It is more logical to assume that cancerigenesis results from the cumulative effect of several forms of irritation. A single acute trauma to the tongue is occasionally alleged to have produced cancer, but this supposition probably has little merit.

Syphilis.—Routine Wassermann tests in our clinic reveal that about 33 per cent of our patients with cancer of the tongue also have syphilis. An incidence (higher in males than in females) of 30 to 40 per cent of syphilis as shown by positive Wassermann reactions is found in most reported series in which this question has been investigated.[6] Beeson,[7] in reporting a general average incidence of 30 per cent of syphilis in cases of cancer of the tongue, found 35 per cent in men and 6 per cent in women and compared this figure with an incidence of positive Wassermann reactions of about 5 per cent which he found in general hospital admissions and of about 7 per cent in cases of cancer in general.

In our series, the average age for cancer of the tongue in syphilitic persons was the same as in nonsyphilitic persons, while Belote found an average age incidence for cancer of the tongue in syphilitic men of 54 years as opposed to 62 years in nonsyphilitic patients. Schreiner

5. Ahlbom, H. E.: Prädisponierende Faktoren für Plattenepithelkarzinom in Mund, Hals und Speiseröhre. Eine statistische Untersuchung am Material des Radiumhemmets, Stockhlom, Acta radiol. **18**:163, 1937.

6. (*a*) Belote, G. H.: Association of Carcinoma of the Tongue and Syphilis as Determined by Positive Serologic Tests, J. A. M. A. **94**:1985 (June 21) 1930. (*b*) Bloodgood, J. C.: Cancer of the Tongue: A Preventable Disease, ibid. **77**:1381 (Oct. 29) 1921. (*c*) Quick, D.: Treatment of Cancer of the Tongue, Brit. J. Radiol. **31**:81, 1926.

7. Beeson, B. B.: Cancer of the Tongue and Syphilis, Urol. & Cutan. Rev. **40**:565, 1936.

and Brown [8] found 40 per cent of cancers of the tongue to be associated with positive Wassermann reactions. It is interesting to compare the incidence of syphilis associated with cancer of the tongue as found by Kaplan [9] (41 per cent) at Bellevue Hospital, New York, where the patients are mainly drawn from an urban population of the less fortunate economic levels, with that of Spencer,[10] who in a distinctly rural population (Boulder, Colo.) found only 1 in 14 patients to have a positive Wassermann reaction. Even though the latter number of patients is small, the smaller incidence of syphilis is highly suggestive.

The immediate etiologic factor in these cases is undoubtedly the chronic glossitis so characteristic of late syphilis. Neither acute syphilis nor the constitutional effect of this disease has any bearing on the etiology of cancer, nor do we believe that there is any specific cancerigenic influence involved. The etiologic significance of syphilitic glossitis probably lies mainly in its chronicity and its frequency. The attendant degenerative changes, such as atrophy of the papillae and leukoplakia, are so characteristic that they have often been considered diagnostic of syphilis.

Nonsyphilitic Glossitis.—One of the most widely known objective symptoms of derangement of function of the gastrointestinal tract is the appearance of the tongue. The brownish coated tongue of chronic constipation and acute indigestion and other forms of chronic glossitis and bald tongue, such as those associated with achlorhydria, pernicious anemia, sprue, pellagra, etc., are well known. More recently, those disorders associated with avitaminosis and dysfunction of the liver have been found to produce profound changes in the lingual mucosa. Many of these degenerative changes are so similar to those produced by syphilis as to be indistinguishable from them except by the Wassermann test. Several of these diseases tend to be self limited, however, by reason of their gravity, so that chronicity, which is essential for the development of cancer, is not characteristic.

Leukoplakia.—In susceptible subjects, chronic irritation of the mucous membrane may result in the development of either leukoplakia or cancer or of both in the same patient. When the two conditions

8. Schreiner, B. F., and Brown, H. F. R.: An Investigation of the Results Obtained in Cancer of the Tongue Treated by Radium and Roentgen Rays, Am. J. Roentgenol. **15**:207, 1926. Schreiner, B. F.: Five-Year End-Results of Radiation Treatment of Cancer of the Oral Cavity, Nasal Pharynx and Pharynx, Radiol. Rev. & Chicago M. Rec. **51**:327, 1929.

9. Kaplan, I. I.: Treatment of Cancer Patients, New York State J. Med. **36**:5, 1936.

10. Spencer, F. R.: Carcinoma of the Tongue: Review of Fourteen Cases, Arch. Otolaryng. **24**:1 (July) 1936.

are associated, the leukoplakia ordinarily precedes the cancer, but one occasionally observes the reverse, that is, leukoplakia developing after the treatment of a cancer of the tongue when none had been present before.

Malignant degeneration may occur within a patch of leukoplakia, or the growth may develop in apparently normal mucous membrane of the tongue at a distance from leukoplakic areas on the cheeks or lips. Preexisting leukoplakia may not be apparent in cases in which a cancerous ulcer has eroded or engulfed a leukoplakic patch. Lingual cancer arising on the basis of advanced leukoplakia commonly begins on the dorsum and is apt to be multiple. We have observed 1 patient in whom three separate primary lesions (not recurrences in a single area) developed on a leukoplakic tongue over a period of about six weeks. Multiple tumors may occur at longer intervals; for instance, a man who was treated at the Memorial Hospital in 1922 for a cancer of the left border of the tongue returned in 1940, at the age of 70, with a cancer of the opposite side of the tongue. In our clinic, some degree of leukoplakia was specifically noted in about 46 per cent of all cancers of the tongue.

Tobacco.—It is difficult to estimate the degree of influence of tobacco in the etiology of cancer of the tongue. In our male group, about 75 per cent of patients admitted the moderate to heavy use of tobacco at some time during their adult life, but this figure loses most of its significance in view of the fact that the general adult male population appears to be addicted in at least as high a percentage. The lesser susceptibility of the female to intraoral cancer has often been ascribed to a lesser indulgence in the tobacco habit. In our series, only 9 per cent of the women admitted smoking, as compared to 75 per cent of the men. Nevertheless, if one considers only the nonsmokers of both sexes, the disease is still more than twice as frequent in the male as in the female.

Teeth and Artificial Dentures.—In the sixth and seventh decades, when the incidence of intraoral cancer is greatest, a large percentage of the general population has suffered dental diseases and defects for prolonged periods. The presence of these dental defects, however, may be coincident with the "cancer age" rather than a direct cause of cancer. As with tobacco, the ubiquity of these dental factors in the whole populations renders it impossible either to affirm or to deny their etiologic significance. In only about 10 per cent of our patients with lingual cancer were the teeth found to be clean and in good repair, and in clinic patients dental defects and sepsis were almost the rule.

In a few instances the association of direct dental trauma with the growth is evident. The most obvious form of dental irritation is the presence of a sharp tooth, broken or worn, or of an ill fitting denture directly in contact with a carcinomatous ulcer, which occurred in

approximately 10 per cent of our patients. In certain instances the experienced observer will suspect that a supposedly guilty tooth or denture may have become "irritating" or "ill fitting" after and because of the development of a cancerous growth, rather than vice versa. Less direct dental abnormalities noted in our patients were advanced dental caries and pyorrhea.

PATHOLOGY

Differentiating, keratinizing squamous carcinomas and relatively nonkeratinizing mucous membrane types of epidermoid carcinoma comprise about 90 per cent of the malignant tumors of the tongue which occur anterior to the circumvallate papillae. About 80 per cent of carcinomas of the base of the tongue are of the nonkeratinizing variety, and in this region anaplastic tumors occur in larger proportion. Transitional cell carcinoma and lymphepithelioma comprise about 20 per cent of tumors at the base. Spindle cell epidermoid carcinomas occur in the tongue, but they are rare. Forms of adenocarcinoma, adenoid cystic adenocarcinoma and mucous gland adenocarcinoma, indistinguishable from various types of gastrointestinal cancer, may occur.

Sarcomas of the tongue are exceedingly rare, except for lymphosarcomas of the lingual tonsillar tissue. The clinical records of the Memorial Hospital contain but 1 case of probable muscle sarcoma. Repeated reference to sarcoma of the tongue may be found in the literature of the last fifty years, but in most cases it seems to us that the histologic verification is far from clear. The only clearly acceptable instances of true malignant myosarcoma recorded in the literature are the 2 described by Cappell and Montgomery,[11] in which the growths occurred in children, as did the one in our case. In any event, sarcoma of the tongue is so rare that it can have little or no influence on the statistics of cancer.

SYMPTOMS, MORBID ANATOMY AND CLINICAL COURSE

In general, lingual cancer tends to be practically symptomless in its early stages. The most common first symptom in our group of cases was the discovery by the patient of the primary lesion itself or of the metastatic node, and in over 50 per cent of the cases there was no complaint except of its physical presence. In the anterior two thirds of the tongue, the growth was usually discovered by the tactile sense as an irregularity or roughening of the mucous membrane.

Occasionally pain is a first symptom in cancer of the tongue, but it is remarkable that this symptom should not be complained of more often, since most benign ulcerated lesions of the tongue are painful, for example, herpes or traumatic ulcers. It is probable that if the tumor

11. Cappell, D. F., and Montgomery, G. L.: On Rhabdomyoma and Myoblastoma, J. Path. & Bact. **44**:517, 1937.

begins in the superficial layers and ulcerates early pain will be an early symptom, but in other instances the growth, even though ulcerated, takes the form of an epithelial covering and thereby protects the underlying sensory nerves from irritation sufficient to cause pain.

In the majority of instances the patient discovers the lesion by the tectile and visual senses alone and not because of any actual discomfort. After this discovery, delay in seeking medical advice is due mainly to the fact that the average layman believes that a serious disease cannot exist in the absence of actual discomfort. Once initiated, the progress of the growth may be so gradual and insidious that it is accepted as a part of a long-standing chronic glossitis or oral dental sepsis. The posterior third, or base, of the tongue has little or no tactile sense and cannot be visualized by the patient, and growths in this region are therefore apt to reach a larger size or even to metastasize before producing symptoms sufficient to induce the patient to seek medical advice.

Other first symptoms, in the order of their frequency, are as follows: the development of palpable cervical nodes, hoarseness, dysphagia or dyspnea (when the base of the tongue is involved) and pain, tenderness or irritation ascribed to sharp teeth or ill fitting dental plates. The average duration of symptoms before admission was about seven months in the series herein reported, as compared to nine months for cancer of the cheek.

The manner of origin and subsequent development of the tumor may vary, depending on its exact site of origin, and we shall consider first the tumors of the anterior two thirds. In this region the most common form is a small, indurated, painless, nontender ulcer arising on the edge of the middle third of the tongue. Palpation reveals that the tumor is larger than it appears on inspection alone. As the lesion increases in size, the surface becomes raised and granular, the ulceration spreads and the infiltration deepens. Finally, the center becomes excavated, and when the growth has reached the size of 2 or 3 cm. in diameter, deep erosion, fissuring and infection commonly occur, with pain and tenderness.

Until the disease has infiltrated about a third of the anterior portion of the tongue or until a fungating tumor 2.5 or 3 cm. in diameter has developed, there is usually little actual discomfort or interference with function. In the later stages, when the muscular body of the tongue has become deeply involved and infiltrated by the growth and by sepsis, the organ lies practically immobile in the floor of the mouth. Surface necrosis is then apt to occur, with repeated hemorrhage due to erosion of the lingual artery or of its larger branches. Pain radiating to the ear or mastoid region, fetor oris and excessive salivation are distressing late symptoms.

Symptoms of Cancer at the Base of the Tongue.—A primary lesion at the base of the tongue is not often discovered by the patient, who is therefore apt to seek medical advice first because of an enlarged cervical node. In the series herein reported, symptoms referable to the tongue or to the pharynx were unrecognized on admission by one third of all patients with cancer at the base of the tongue, since, even when present, such symptoms as slight soreness, dysphagia, hoarseness or dyspnea were apt to be vague and misleading. A cancer at the base of the tongue may ulcerate and reach a size of 3 cm. or more without causing any particular noticeable local symptoms.

In over 30 per cent of cases of growths of the posterior third of the tongue, the referring physician had not discovered the primary lesion but had suspected cancer because of cervical adenopathy. A careful examination of patients referred because of cervical lymphadenopathy (nodes 3 to 4 cm. in diameter or even larger) often discloses a primary lesion in the base of the tongue less than 1 cm. in diameter, though in most instances it is over 2.5 cm. in diameter when the first diagnosis of cancer is made.

Morbid Anatomy.—Cancer of the tongue is almost always of epithelial origin and therefore begins on the surface. Unfortunately, one rarely has an opportunity to observe and describe the disease in its earliest stages. In our clinic, in the rare instances when the lesions were less than 5 mm. in diameter, they almost all appeared as slightly ulcerated fissures in the center of preexisting leukoplakic patches (fig. 2). It is certain, however, that the disease does not always begin in this manner. When the growth does not originate in a leukoplakic patch, it is probable that it begins as a microscopic submucous nodule and that the earliest departures from the normal are so slight as to preclude a diagnosis by physical examination until the growth has reached a size of 6 to 10 mm., with definite induration and ulceration.

Most of the earlier lesions are from 1 to 2 cm. in diameter when first discovered and consist of a superficial, indurated plaque, slightly raised above the surface of the tongue, ulcerated in its center, with an irregular, nodular, coarsely granular surface (fig. 3). In such lesions the induration extends several millimeters beyond the edge of the ulcer and the infiltration reaches a depth of 0.5 to 1 cm.

There may be considerable variation in the anatomy of tumors which have reached a size of 2 to 2.5 cm. in diameter. At one extreme may be found papillary fungating lesions with only moderate infiltration, often slightly pedunculated, with marked eversion of the mucous membrane at its borders. The degree of fungation from the surface is usually inversely proportionate to the depth of the infiltration. At the other extreme are the deeply infiltrating and excavating lesions which

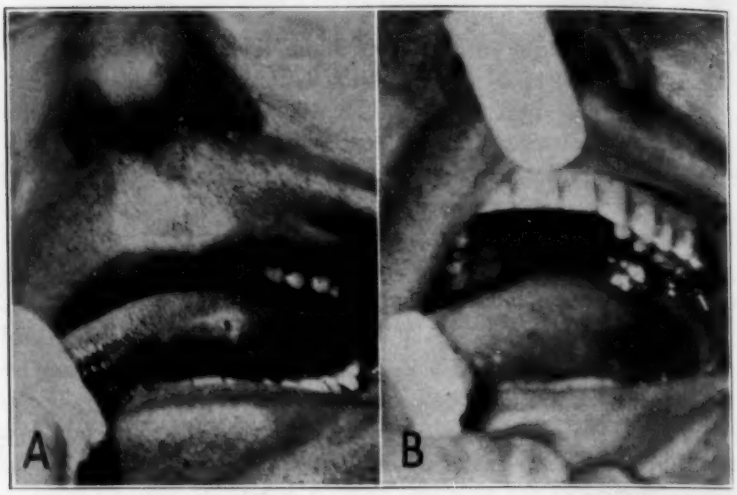

Fig. 2.—Very early cancer of the tongue arising in the center of an area of leukoplakia in the middle third of the lateral border (*A*). At this stage the chances of metastatic invasion of the cervical nodes are slight, and cure is almost certain with either irradiation or surgical treatment. In this case, after biopsy the treatment was by the implantation of one radon seed of about 2 millicuries. *B*, healed condition. The patient has remained well for about eight years.

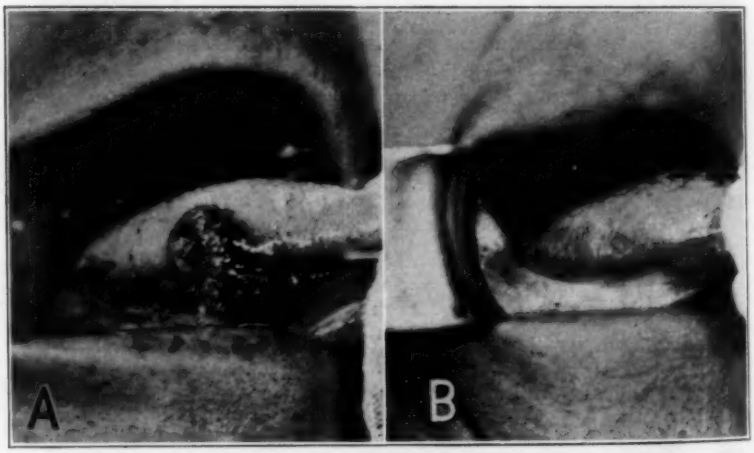

Fig. 3.—The average cancer of the tongue on the patient's admission to the hospital presents an ulcerated granular lesion 2 to 2.5 cm. in diameter on the lateral border of the tongue in the middle third (*A*). At this stage, even though the lymph nodes are not palpably enlarged, metastases are actually present on admission in about 10 to 15 per cent of all cases, as shown by the later clinical course. The preferable form of treatment for the primary lesion is irradiation. *B*, healed condition after application of peroral roentgen radiation supplemented by radon seeds. Since no cervical metastases were palpable, no treatment was given to the neck. The patient has remained well for about six years.

begin to erode the tongue substance in the early stages of infiltration. Midway between these extremes are found tumors which produce only moderate alteration of the normal contour of the lingual surface, although they ulcerate superficially and infiltrate deeply.

In other clinical forms the lesion may assume the character of a superficial ulceration which advances mainly at the edges, eroding the mucous membrane over an area 2 to 3 cm. in diameter without infiltrating the lingual substance to a greater depth than 3 to 4 cm. In some instances the growth apparently arises in the deep layers of the mucous membrane or in fissures and extends and infiltrates deeply, so that a large tumor may occupy the body of the tongue with little or no surface ulceration. In the so-called scirrhous form the involved

Fig. 4.—Cancer of the dorsum of the tongue is usually associated with leukoplakia, and there may be multiple primary lesions. The dorsum of the tongue is readily accessible to treatment by irradiation, and the prognosis is good except for the possibility of the development of additional growths in other areas. This patient had a cervical metastatic node in the left side of the neck, which after aspiration biopsy was treated by fractionated roentgen irradiation and implantation of radon seeds. The patient has remained well for over five years.

portion of the tongue is shrunken, sometimes to such an extent that in the advanced stages of the disease the whole organ seems to have disappeared.

Cancer developing on the basis of advanced leukoplakia may appear as a papillary, warty, nonulcerated growth, as an indurated, slightly ulcerated fissure in a leukoplakic patch or as a deep red superficial granular ulcer surrounded by leukoplakia (fig. 4). When the cancer develops on the basis of a long-standing syphilitic glossitis (both superficial and interstitial), the tongue may be so swollen and edematous

that the jaws cannot be completely closed. In such instances the swollen bulk of the tongue may be due mainly to sepsis while the mass of the actual cancer is comparatively small (fig. 5).

In the advanced stages more than one clinical variety may be present. The entire tongue may be infiltrated and boardlike, with surface ulceration over one or more areas 1 to 2 cm. in diameter; in other instances the growth may infiltrate deeply from its point of origin and appear on the surface in one or more additional areas by perforation of the mucosa from below.

Metastases.—The comparative incidence of metastases on admission to the hospital with the more common forms of intraoral cancer is shown in table 1. In the series of cancers of the tongue reported here, the

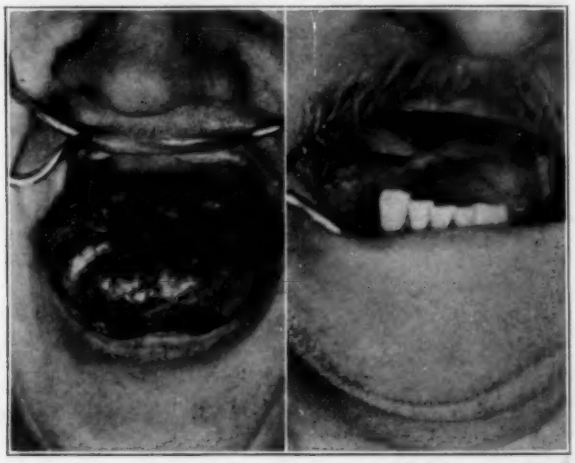

Fig. 5.—Diffuse involvement of the tongue by cancer and interstitial syphilitic glossitis. Such lesions are not suitable for treatment by irradiation, and if the tongue is movable, they are sometimes best dealt with by subtotal glossectomy. This patient died of cervical metastases after several months without local recurrence following subtotal glossectomy.

TABLE 1.—*Incidence of Cervical Metastases of Intraoral Cancer Observed at the Memorial Hospital*

Primary Lesion	Metastases on Admission	Metastases after Admission	Total Metastases	None at Any Time
Tongue	35%	25%	60%	40%
Lip	25%	8%	33%	67%
Cheek	45%	10%	55%	45%
Nasopharynx	77%	4%	81%	19%

incidence of metastases on admission was about 39 per cent. An additional 24 per cent subsequently had metastases, making a total of 62 per cent with metastases at some time during the course of the disease.

The group of lymph nodes earliest and most frequently involved is the upper deep cervical (55 per cent), which is centered about at the bifurcation of the common carotid artery (fig. 6). This area was eventually involved in 80 per cent of all cases of metastasizing cancer of the tongue in this series. When initial involvement of the cervical nodes is on the side of the neck opposite the primary lesion, the upper deep cervical nodes are almost always the first to be invaded. In the cases under consideration, bilateral metastases occurred in about 25 per cent of all lesions which metastasized. The sites next often involved, in the order of their frequency, are the submaxillary triangle (15 per cent) and the midneck (7 per cent). As the disease progresses, it extends to the other groups of nodes, and after the upper deep cervical nodes have been invaded, one should always be on the watch for enlarged nodes in the lower deep cervical region or in the posterior triangle of the neck.

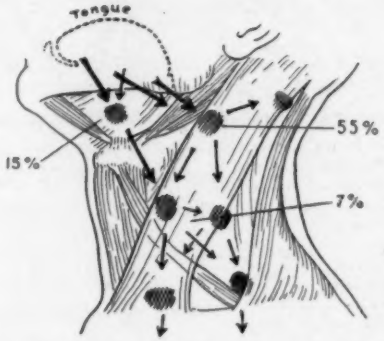

Fig. 6.—Pathways of metastasis in cancer of the tongue. The figures express the frequency of initial involvement in certain areas.

Dissemination below the clavicle to the viscera or other soft parts and to bone is far more frequent in cancer of the tongue than in cancer of the lip or cheek.[12] Visceral metastases are particularly likely to follow growths of the base of the tongue, where anaplastic tumors are common. In the autopsy records of the Memorial Hospital, it has been found that of about 68 patients dead of lingual cancer, 12 (18 per cent) had visceral metastases with the distribution shown in table 2. Ewing [13]

12. (*a*) Crile, G. W.: Carcinoma of Jaws, Tongue, Cheek and Lips, Surg., Gynec. & Obst. **36**:159, 1923. (*b*) Gernes, C.; Breton, A., and Boury, M.: Cancer du coeur secondaire à un épithélioma de la langue cliniquement guéri par l'application de radium: réflexions, Bull. Assoc. franç. p. l'étude du cancer **26**:58, 1937. (*c*) Lenz, M., and Sproul, E.: Carcinoma of the Tongue, Am. J. Surg. **35**:102, 1934. (*d*) Spencer, W. G., and Cade, S.: Diseases of the Tongue, Philadelphia, P. Blakiston's Son & Co., 1931.

13. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

reported a case of diffuse permeation of pulmonary lymphatics from squamous carcinoma of the tongue.

DIAGNOSIS

A tentative diagnosis of cancer of the tongue is not difficult in the average case. Whenever chronic ulcers or indurated tumors occur in the tongue or any other part of the oral cavity, cancer should be suspected. Examination of the anterior two thirds of the tongue is easily performed under ordinary lighting assisted by the palpating finger. Examination of the base of the tongue should be performed by inspection with a headlight and a throat mirror, supplemented by careful palpation.

Biopsy.—If a suspicious lesion is found, a biopsy should always be made at the time of the first examination. In any case, there is no excuse for a temporizing or passive attitude in the presence of a chronic

TABLE 2.—*Incidence of Distant Metastases from Lingual Cancer Observed at the Memorial Hospital*

Total number of autopsies		67
Number showing distant metastases		12 (18%)
Lungs	7	
Liver	4	
Mediastinal nodes	4	
Pericardium	4	
Pleura	4	
Diaphragm	2	
Ribs and sternum	1	
Humerus	1	

ulcer of the tongue. Even though therapeutic tests may be subsequently indicated in the form of antisyphilitic therapy, sodium perborate mouth washes for Vincent's ulcers or extraction of teeth, there is no contraindication to making immediate biopsy.

A survey of both the past and the present day literature will reveal that there is no uniformity of opinion in regard to the necessity and justification for biopsy in cases of cancer of the tongue. Spencer and Cade [12d] called attention to the fact that the common tendency to give the patient a chance by treating an undiagnosed lesion as benign in many instances gives the cancer, rather than the patient, a chance. They also made the rather equivocal statement that a biopsy specimen should be taken, provided that "it is not detrimental to the patient." One might ask what possible detriment to the patient could result from taking a biopsy specimen in comparison to the absolutely fatal consequences of an undiagnosed and untreated cancer of the tongue. What could be more detrimental than the misfortune of treating syphilis or tuberculosis by irradiation or excision of the tongue under a mistaken diagnosis of

cancer? Without biopsy, most tuberculous and gummatous lesions of the oral cavity would be treated as cancer in the average otherwise competent cancer clinic. There is no way to make cancer a safe disease, but probably the weakest and most futile gesture which can be made toward this end is the simple omission of a biopsy.

One biopsy with negative results does not necessarily disprove the presence of cancer. The more intelligently the tissue fragment is removed from the indurated edge of the ulcer, the more dependence can be placed on the histologic report. In any case, the ulcerated surface of a malignant ulcer may be covered by exuberant simple granulation tissue, and therefore, if the clinical appearance of the lesion so indicates, when a biopsy gives negative results the examination should be repeated at least once. A safe precept is: In the presence of a suspicious lesion, *always rule out cancer first.* This usually means the removal of a biopsy specimen.

A biopsy specimen from a fungating cancer of the tongue is usually best taken by a biting forceps, a fragment about 3 to 5 mm. in diameter being removed. If the lesion is deeply infiltrating, with a depressed, firm center, a scalpel may be used to remove a small wedge of tissue of about the same diameter. A lesion at the base of the tongue often cannot be approached by direct vision, and the specimen is preferably removed by a curved specimen forceps guided by a throat mirror.

Cervical Adenopathy.—An essential finding in the diagnosis of cervical metastases is palpable enlargement of the lymph nodes. Without such enlargement, it must be assumed for all practical purposes, at least for purposes of record, that such metastasis has not as yet taken place. Even though present, enlargement of lymph nodes within the area of drainage of an infected cancer may be due to pyogenic infection only, and in such cases the cancer itself may not have spread beyond the borders of the primary lesion. It must also be realized that lymph nodes are not necessarily diseased or in any way abnormal simply because they are palpable.

About 30 per cent of all cancers of the base of the tongue in the clinic at the Memorial Hospital are referred because of cervical lymphadenopathy with the primary lesion undiscovered. Not infrequently, cervical nodes have been excised for biopsy and the patients referred with a diagnosis of "cancer of the neck." In all cases in which the complaint is only of cervical lymphadenopathy, the oral cavity, the base of the tongue, the nasopharynx and the pharyngeal walls should be carefully examined for a primary lesion. It should be remembered that *most cervical adenopathies in the adult are malignant and probably metastatic from cancer primary in the oral cavity or the oral and nasal pharynges.*

Delay in Diagnosis.—Unfortunately, the physician whom the patient first consults is often responsible for a serious delay in diagnosis. The significance of such diagnostic errors is due not only to the frequency with which they occur but also to the fact that the patient, his fears quieted, may procrastinate unusually long before seeking a second opinion. The average time between the patient's first visit to a physician and a correct diagnosis was five months in the present series, a figure which agrees fairly well with reported averages.[13a] In over 10 per cent of cases, antisyphilitic treatment had been given for periods varying from two months to two years (average six months) under a mistaken diagnosis of gumma. In about 6 per cent of these instances, the physician had noted the primary lesion and had applied a topical remedy, usually cauterization by silver nitrate, with an average delay in correct diagnosis of three months. Curiously enough, cancer of the base of the tongue is often confused with chronic tonsillitis. In a period of four years at the Memorial Hospital, 8 patients were referred after tonsillectomy for the relief of symptoms undoubtedly caused by the presence of a bulky cancerous ulcer at the base of the tongue.

The members of the dental profession are also responsible for some delay in diagnosis. In about 5 per cent of our series the patients had first consulted a dentist and had had teeth extracted in the neighborhood of the tumor itself, believing that the lesion of the tongue was simply dental trauma. The probable nature of the disease was immediately recognized by the dentist in less than 10 per cent of these cases.

Differential Diagnosis.—The diseases most apt to offer some difficulty in differential diagnosis are, in the order of their importance, syphilis, tuberculosis, papilloma, superficially ulcerated or fissured leukoplakia and simple granuloma (Vincent's angina, trauma, etc.). Less common conditions sometimes confused with cancer of the tongue are glossitis rhombica mediana and muscle xanthoma. Such conditions as hemangioma, lymphangioma and papillary fibroma resemble cancer so little that they never should be confused with it.

Syphilis.—For several reasons, syphilis is responsible for more delay and confusion in the diagnosis of lingual cancer than is any other condition. First, a great deal of stress has been placed on the diagnosis of syphilis in medical education. Second, gumma and lingual cancer present about the same clinical appearance (fig. 7). Third, about one third of all patients with lingual cancer also have syphilis.

Since in medical education the fact is stressed that syphilis may manifest itself in a variety of forms, it is perhaps natural that the physician should assume syphilis to be the sole cause of a chronic ulcer when the

13a. Rahausen, A.: Cáncer en la cavidad bucal, Santiago, Chile, Instituto nacional del radium, 1936. Lane-Claypon.[2]

Wassermann reaction is positive. This assumption leads to the most frequent and tragic errors in the diagnosis of lingual cancer. In our clinic, we find that prior to admission more than 10 per cent of patients with cancer of the tongue have received antisyphilitic treatment for an average period of six months before the physician finally has realized that syphilis alone was not responsible for the lesion. *In a case of chronic ulcer of the tongue, a positive Wassermann reaction does not disprove the presence of cancer,* since syphilis and cancer of the tongue coexist in about one third of all cases, as has already been mentioned. As a matter of fact, the presence of a positive Wassermann reaction strongly suggests that an associated chronic ulcer of the tongue is cancer rather than any other condition.

Since gumma of the tongue is so rare (the incidence is less than 1 per cent of that of cancer of the tongue), it seems illogical to employ the

Fig. 7.—Gumma of the tongue is a rare disease and may closely simulate cancer. The diagnosis should be made only after exclusion of cancer by repeated biopsies and the complete healing of the lesion within a month under antisyphilitic treatment. A lesion of the tongue which persists for more than that time under aggressive antisyphilitic treatment is not a gumma.

therapeutic test without first making a biopsy. It is certainly unwise to persist in the therapeutic test for longer than three weeks, for it has been our experience that a gummatous ulcer of the oral mucous membrane will invariably heal within that time under aggressive antisyphilitic therapy. The clinical appearance of long-standing syphilitic glossitis with leukoplakia is not markedly altered even by heavy and long-continued antisyphilitic therapy, and the therapeutic test is therefore of no value in these cases.

Tuberculosis.—Tuberculous ulcers of the tongue are often confused with cancer and as such are referred to a cancer clinic. The relative frequencies of cancer, tuberculous ulcers and gumma of the tongue, according to the admission records of the Memorial Hospital, are, respectively, about 100, 3 and less than 1. Tuberculous ulcers are usually

on the dorsum of the tongue but occasionally on the borders or at the tip. They ordinarily present a smoothly granular, yellowish, unhealthy base with little or no overgrowth of tissue, in contrast to the coarsely granular appearance of carcinoma (fig. 8). Tuberculous ulcers are more apt to be painful and tender, with little or no induration. A diagnosis is made with the aid of biopsy (preferably repeated), a roentgenogram of the chest and examination of the sputum. Such lesions of the tongue or other oral mucous membranes are almost invariably secondary to demonstrable pulmonary tuberculosis. A correct diagnosis is especially important, since the proper treatment for cancer is almost the worst possible treatment for tuberculosis, and vice versa.

Fig. 8.—Tuberculous ulcers may occur on the borders, the tip or the dorsum of the tongue. They may closely simulate cancer in appearance but are usually both painful and tender. The diagnosis is made by biopsy, roentgen examination of the chest and examination of the sputum.

Papilloma.—Any epithelium of the stratified squamous type may give rise to papilloma, and that of the tongue is no exception. Such lesions usually are the result of some form of chronic irritation to which the tissue response is a relatively benign overgrowth. In certain instances, papilloma may be an intermediary stage or a precancerous condition or may contain areas in which the transition is complete and true cancer is already present. Papilloma of the tongue most commonly occurs at the tip or on the borders. We have never seen it at the base. The lesions are usually papillary but may be either sessile or slightly pedunculated.

Leukoplakia.—Leukoplakia is a common condition of the oral cavity. In a careful examination and analysis of 200 patients (100 men and 100

women) over 45 years of age without intraoral cancer at the Memorial Hospital, demonstrable leukoplakia was found in over 50 per cent of the men and in 10 per cent of the women. Leukoplakia so advanced as to be obvious on even casual examination may be found in about 15 per cent of otherwise normal men over 45 years of age.

Only the advanced fissured or verrucous types of leukoplakia offer any problem in differential diagnosis. In these lesions, cancer may be present at any point, and a decision as to the treatment may be somewhat difficult. Biopsy specimens should, of course, be taken from the most suspicious areas. If these are noncancerous, aggressive treatment for leukoplakia had best be carried out as a prophylaxis against cancer.

Simple Granuloma.—A diagnosis of simple granuloma should never be made in the case of a chronic ulcer of the tongue without repeatedly negative results of biopsies and/or a prompt healing of the lesion under simple measures. The biopsy may be withheld temporarily if there is a history of competent and recent acute trauma, such as biting of the tongue, or if a painful tender ulcer, such as those present in herpes or Vincent's disease, suddenly appears. If such an ulcer persists longer than two weeks, a biopsy is definitely indicated.

The Foliate Papillae.—These structures are situated on the edge of the tongue just opposite and anterior to its junction with the anterior tonsillar pillar (fig. 1). The foliate papillae appear as variable but usually slight elevations in the surface contour, marked by several vertical fissures. Their color is ordinarily somewhat deeper red than the surrounding mucosa, and on a casual examination they may even resemble superficial ulcers. In cancerophobia, these areas are frequently noted, and with repeated examination and palpation by the patient the difference in color may become more marked. Therefore, in the differential diagnosis of cancer of the tongue in an apprehensive patient, these areas assume considerable significance. Lacassagne [14] and others have discussed this question in some detail. When cancer arises primarily in this area, its early stages may closely resemble a slightly inflamed foliate papilla.

Glossitis Rhombica Mediana.—This condition is most often found in middle-aged men and consists of an indurated, nonulcerated, painless superficial ovoid or rhomboid mass situated in the midline of the dorsum of the tongue, just anterior to the circumvallate papillae in the apex of the V. The appearance and especially the position are diagnostic. We have never seen cancer arise at this point in the tongue. No treatment is indicated for glossitis rhombica mediana except in the presence of

14. Lacassagne, A.: Radium Treatment of Cancer at the Curie Institute, Paris, New York, Thos. Nelson & Sons, 1931.

cancerophobia, in which the lesion may be surgically excised. A series of 11 cases has been reported from the Memorial Hospital.[15]

Fibroma.—Papillary fibroma, a pedunculated smooth lesion usually 2 to 4 mm. in diameter, commonly occurs at the tip of the tongue, apparently more often in females than in males. The benign character of this lesion is evident, and the treatment is by local excision.

Angioma.—Hemangioma and lymphangioma should offer no difficulty in differential diagnosis at this time, but lymphangioma formerly was often mistaken for cancer of the tongue.

GENERAL PRINCIPLES IN THE TREATMENT OF CANCER OF THE TONGUE

There is considerable difference of opinion as to the most effective methods of treatment of cancer of the tongue. At one extreme are found those who advise surgical excision of the primary lesion (either by scalpel or by endothermy) and neck dissection for cervical metastases (Harmer;[16] Morrow;[17] New;[18] Truesdale;[19] Simmons[20] and others). Under this purely surgical management the operative mortality is high. Among various authors, the mortality is reported to be in the neighborhood of 25 per cent of the patients so treated. In their writings these authors either omit any specific mention of irradiation or concede its usefulness only in the treatment of recurrent or hopelessly advanced lesions, whereas in institutions where there are adequate facilities for irradiation and surgeons experienced in their application, there is a general agreement that irradiation, either alone or combined with conservative surgical treatment is the most applicable and generally useful method of treatment for the primary lesion (Berven;[21] Quick;[6c] Roux-Berger;[22] Tailhefer;[23] Coutard,[24] and others).

15. Martin, H. E., and Howe, M. E.: Glossitis Rhombica Mediana, Ann. Surg. **107**:39, 1938.

16. Harmer, W. D.: Cancer of the Tongue, Brit. J. Surg. **15**:661, 1928.

17. Morrow, A.: Cancer of the Tongue, Ann. Surg. **105**:418, 1937.

18. New, G. B.: Cancer of the Tongue and Lower Jaw, Tr. Am. Laryng., Rhin. & Otol. Soc. **41**:1935, 1935.

19. Truesdale, P. E.: Cancer of the Tongue, Ann. Surg. **78**:461, 1923.

20. Simmons, C. C.: Treatment of Oral Cancer, Am. J. Roentgenol. **26**:5, 1931.

21. Berven, E. G. E.: Résultats du traitement radiothérapique des cancers de la cavité buccale et du pharynx, Gaz. méd. de France (supp. Radiol.), 1935, p. 377: Radiological Treatment of Malignant Tumours of the Oral Cavity and Pharynx, Acta radiol. **18**:16, 1937.

22. Roux-Berger, J.: Cancer de la langue, Bull. et mém. Soc. nat. d. chir. **58**: 1343, 1932.

23. Tailhefer, A.: Traitement chirurgical des adénopathies du cancer de la langue. Resultats eloignés, Mém. Acad. de chir. **62**:975, 1936. Quick.[6c]

24. Coutard, H.: Roentgen Therapy of Epitheliomas of Tonsillar Region, Hypopharynx and Larynx from 1920 to 1926, Am. J. Roentgenol. **28**:313, 1932.

There is also divergence of opinion regarding the treatment of the cervical metastases. Some investigators urge that surgical measures be used in all operable cases, irradiation being considered as a last resort.[25] Others recommend irradiation in certain instances and report cases in which irradiation alone resulted in permanent regression of the metastases.[26]

Whether surgical or radiation methods or combinations of the two are used for cancer of the tongue, these procedures are more difficult to apply and their complications are more serious in the tongue than in either the lip or the cheek. The local involvement of the tongue is seldom limited to the more accessible free portions of the tip and borders of this organ, which are fairly accessible to any method of treatment. Early in its course the disease tends to invade neighboring structures, such as the floor of the mouth or the tonsillar pillars, and such comparatively inaccessible and inoperable areas as the base or the deep extrinsic musculature of the tongue. In formulating a system of treatment for an unselected group of cases, one must therefore accept at the outset the fact that a relatively small proportion of all patients with cancer of the tongue may be considered operable when first seen. It follows, therefore, that surgery alone can never be the solution of this problem.

It is unfortunate that the current medical literature should still contain reports attempting to prove the superiority of one method alone—either radiation or surgical therapy—in the treatment of this disease. In our opinion, any such partisan attitude is entirely out of place in the management of so serious a problem as lingual cancer. At the Memorial

25. Cutler, M., and Buschke, J. F.: Cancer: Its Diagnosis and Treatment, Philadelphia, W. B. Saunders Company, 1938. Eggers, C.: Cancer Surgery: Value of Radical Operations for Cancer After Lymphatic Drainage Area Has Become Involved, Ann. Surg. **106**:668, 1937. Fischel, E.: Rational Therapy for Cancer of the Lower Lip, Am. J. Cancer **15**:1321, 1931. Kennedy, R. H.: Epithelioma of the Lower Lip: Suggested Routine for Treatment with Description of Operative Excision of Submental and Submaxillary Lymph Nodes, Ann. Surg. **106**:577, 1937. Searby, H.: Treatment of Carcinoma of the Tongue, M. J. Australia **2**:210, 1926. Wangensteen, O. H., and Randall, O. S.: Treatment and Results in Carcinoma of the Lip: Report of One Hundred and Thirty Cases, Am. J. Roentgenol. **30**:75, 1933. Tailhefer.[23]

26. (*a*) Coutard, H.: Results and Methods of Treatment of Cancer by Radiation, Ann. Surg. **106**:584, 1937. (*b*) Duffy, J. J.: Cervical Lymph Nodes in Intraoral Carcinoma: Surgery or Irradiation? Am. J. Roentgenol. **39**:767, 1938. (*c*) Lewis, F. O., in discussion of Symposium on Intraoral Cancer, Am. J. Roentgenol. **26**:39, 1931. (*d*) Neill, W., Jr., in discussion of Symposium on Intraoral Cancer, ibid. **26**:39, 1931. (*e*) Pfahler, G. E., in discussion of Symposium on Intraoral Cancer, ibid. **26**:39, 1931. (*f*) Welch, C. E., and Nathanson, I. T.: Life Expectancy in Malignant Disease: II. Carcinoma of Lip, Oral Cavity, Larynx and Antrum, Am. J. Cancer **31**:238, 1937.

Hospital our staff is composed of surgeons who administer or direct each detail of the treatment, whether by surgical intervention, radium or roentgen rays. The surgeon-radiologist, therefore, uses his unbiased judgment as to the nature and order of these several procedures.

In the treatment of cancer of the tongue, three distinct problems must be considered: (1) the hygienic care of the oral cavity before and during treatment; (2) the treatment of the primary lesion, and (3) the treatment of cervical metastases. Each of these problems must be dealt with by a separate and distinct set of procedures.

General Hygienic Measures.—Before instituting treatment, prompt measures should be taken to improve the oral hygiene. The teeth should be cleaned by a dentist and the patient instructed in the use of a toothbrush. Sharp teeth, especially if in contact with the lesion, should be filed smooth or possibly extracted. If the treatment is to include heavy irradiation, however, it is often safer to leave the teeth in place, if possible, than to extract them, because of the danger of osteomyelitis—a complication which we shall presently discuss in more detail.

A normal hygienic condition of the oral cavity is maintained in great part by the constant flow of saliva. In many acute inflammatory disorders of the oral cavity and especially in those following irradiation, the amount of saliva is markedly decreased and the normal washing or flushing action of the saliva is lost. Therefore, the oral cavity should be irrigated frequently (every one or two hours) with copious mildly alkaline saline solutions (1 to 2 quarts of warm water with 1 teaspoon each of sodium bicarbonate and sodium chloride). Sodium perborate or zinc peroxide solution or other oxygenic mouth washes every two to four hours are also of great value during the radiation reaction and until the tongue has entirely healed. Daily visits to the clinic are advisable during the first few weeks of treatment. A successful result often depends to a considerable degree on a vigorous combating of oral sepsis, which is an important complication under any form of treatment.

The feeding problem may be one of the most important factors in successful treatment. It is sometimes undesirable for the patient to take food by mouth even though he is able to do so, because the limitation in movement of the inflamed tongue may induce a partial retention of the food in the mouth, where it tends to putrefy and increase the sepsis. For these reasons it is often advisable to administer most of the nutriment by nasal catheter during the period of the acute radiation reaction.

In all cases in which radiation reactions or open operative wounds are present in the mouth, vitamin therapy (especially B and C) and the administration of liver extract, either perorally or intramuscularly,

are of great value, since an inadequate intake of these substances will tend to produce lesions of the mucous membrane of the oral cavity.

The question often arises as to whether the attendant syphilis, which commonly is first diagnosed at the same time as the cancer of the tongue, should be treated concurrently with the tumor. In our opinion, the presence of a positive Wassermann reaction with an uncomplicated noninfected cancer of the tongue does not call for antisyphilitic treatment in the beginning. If there is a great deal of glossitis and oral sepsis, it is probable that the attendant syphilis is responsible for at least a part of these complications, and in such instances marked improvement in oral hygiene may follow the administration of mild antisyphilitic treatment. Beyond this point antisyphilitic treatment should not be pushed until after the cancer is under control and healing has taken place.

TABLE 3.—*Methods Used at the Memorial Hospital for Treatment of the Primary Lesion of Cancer of the Tongue*

A.	Radon seeds alone for very small early lesions
B.	Fractionated peroral roentgen irradiation supplemented by radon seeds—the most useful method for all except the very small growths of the anterior two thirds of the tongue
C.	Fractionated roentgen irradiation through the neck followed by supplementary radon seeds for cancer of the base of the tongue.
D.	Radon seeds ("overdosage") followed in 5 to 10 days by partial glossectomy. This method is indicated only for a limited number of bulky, fungating, partly necrotic tumors.
E.	Variations in technic:
	1. Roentgen irradiation alone. This may be successful with a limited number of very radiosensitive tumors. Supplementary interstitial irradiation is probably indicated in all cases
	2. Low voltage, lightly filtered peroral roentgen irradiation. This form of treatment should be limited to the very superficial growths on the anterior portion and dorsum of the tongue
	3. Surgical excision alone without either preliminary or postoperative irradiation. This procedure has a very small field of usefulness and should be limited to the fungating papillary tumors at the tip of the tongue

TREATMENT OF THE PRIMARY LESION IN CANCER OF THE TONGUE

In our opinion, the treatment of the primary lesion in the tongue should depend mainly on radiation, and if the lesion can be controlled by this means alone, the result most nearly approaches the ideal. Wide surgical excision would undoubtedly control a fair percentage of early accessible lesions, but this procedure is attended by marked functional disability and in any case is applicable only to the operable minority. It is probable that the majority opinion at this time favors irradiation rather than surgical treatment. A combination—irradiation followed by operation immediately or for late complications—is an indispensable method in certain instances. Since several technics or combinations for the treatment of the primary lesion in cancer of the tongue are used in our clinic, each had best be described separately. These methods and their main indications are given in table 3.

Radon Seed Implantation.—Gold radon seeds, in our opinion, are almost universally the best form of applicator for interstitial irradiation. In many clinics, radon or radium needles are considered superior to seeds (Berven;[21] Regaud;[4c] Spencer and Cade,[12d] and others). In most clinics where such opinions are held, radon seeds are not generally available or have never been extensively used, and we believe that where both are available the preference for seeds is rather uniform.

The surgeon who has become accustomed to the use of seeds and who then witnesses the introduction and suturing of needles into the tongue will be struck by the excessive trauma, which could be avoided, and the cruel necessity for maintaining these foreign bodies sutured into the tongue for eight or ten days, as compared to the rapid, painless introduction of seeds with use of local or short general anesthesia. In small superficial lesions (0.5 to 1.5 cm.) of the anterior two thirds of

TABLE 4.—*Millicuries in Gold Seeds Required to Deliver Specified Doses to Masses of Various Diameters.*

	Diameter of Mass, Centimeters											
Skin Erythema Doses	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
	Number of Millicuries											
5	1.0	2.5	4.0	7.5	10	12	14	17	20	27	35	45
6	1.2	3.0	4.8	9.0	12	14	17	20	24	32	42	54
7	1.4	3.5	5.6	10	14	17	20	24	28	38	49	63
8	1.6	4.0	6.4	12	16	19	23	27	32	43	56	72
9	1.8	4.5	7.2	14	18	22	26	31	36	49	63	81
10	2.0	5.0	8.0	15	20	24	29	34	40	54	70	90
11	2.2	5.5	8.8	17	22	26	32	37	44	59	77	99
12	2.4	6.0	9.6	18	24	29	35	41	48	65	84	108

the tongue, seeds may be implanted directly into the growth from the mucosal surface with the region under local anesthesia. If the growth is larger or if there is a great deal of infection and tenderness, conduction anesthesia or general anesthesia may be indicated.

If radon seeds are used alone in a single application, the dosage should be calculated so as to deliver about 10 threshold erythema doses to all parts of the tumor. The number of millicuries in seeds required to deliver specific tissue doses to masses of various sizes is given in table 4. So many factors enter into the selection of the interstitial dosage that this question must remain partly empiric. In the smaller tumors (requiring about 5 or 6 millicuries) it is sometimes most practical to implant a single dose of seeds. For the larger tumors the principle of protraction or division of the dose is of definite advantage. In this divided dose method, seeds are implanted every five to seven days in fractions of the dose. The total dosage of seeds in the latter technic must be increased by 25 to 50 per cent over that required in a single application. Total doses approaching or exceeding 20 millicuries destroyed in the tongue are apt to produce marked reactions and serious

complications, and such heavy dosage should not be employed except by those who are experienced in this method of therapy.

The surface of the tongue through which the seeds are implanted should be thoroughly dried first and then painted with tincture of iodine (fig. 9). The introduction of infection during implantation or needling is one of the most potent factors in the production of subsequent radionecrosis. If the surface is recontaminated during implantation, it should be resterilized before proceeding. Ordinarily, seeds of 1.5 to 2.0 millicuries are the most suitable, but their individual strengths should depend somewhat on their number and distribution.

Even with the strictest sterile precautions, it is not always possible to avoid the introduction of infection when seeds are implanted directly through the oral mucous membrane. For the larger lesions of the middle third of the tongue and for all lesions at the base of the tongue, the readily sterilized skin of the submental or suprahyoid region may

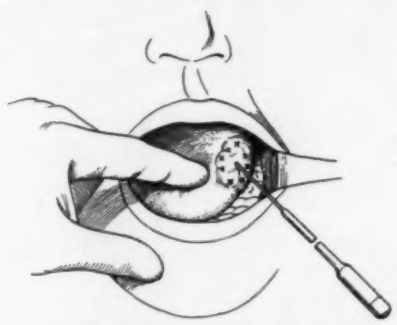

Fig. 9.—Implantation of radon seeds in cancer of the tongue.

be used as the avenue of approach. The midline of the submental region from the symphysis to the hyoid contains no deep structures liable to injury by the implanting trocar needle. The skin at the point of the intended puncture is infiltrated with solution of procaine hydrochloride, and the needle is then slowly advanced through the deep tissues along its path up to the tumor. Through a stab wound in the skin, the implanting trocar needles are inserted and guided in their deep approach into the tumor by a palpating finger within the mouth (fig. 10). After the implantation of larger doses of radon seeds (15 millicuries or more) into the tongue, protective shields may be constructed to spare adjacent normal structures from at least a portion of the unwanted effects of radiation.[27]

Fractionated Peroral Roentgen Radiation Supplemented by Radon Seeds.—This combination of radiation technics is probably the most useful and practical method so far devised in the treatment of the pri-

27. Ackerman, A. J.: Protective Shields in Radiation Therapy of Intraoral Cancer, Am. J. Roentgenol. **38**:746, 1937.

mary lesion of cancer of the tongue. The value of the protracted or divided dose principle of roentgen irradiation for intraoral and pharyngeal cancer has been widely accepted, and no detailed discussion of its merits will be undertaken in this report. The main advantage of the fractionated over the massive dose principle is that with the former, the selective action of radiation is increased, so that a greater destructive effect is produced in the cancer with a lesser degree of harmful action on the normal tissues of the tumor bed. The main objection to the use of this principle in the treatment of cancer of the anterior two thirds of the tongue is that if the skin of the cheeks is used as the portal of entry the jaws and dental apparatus are so heavily irradiated that certain

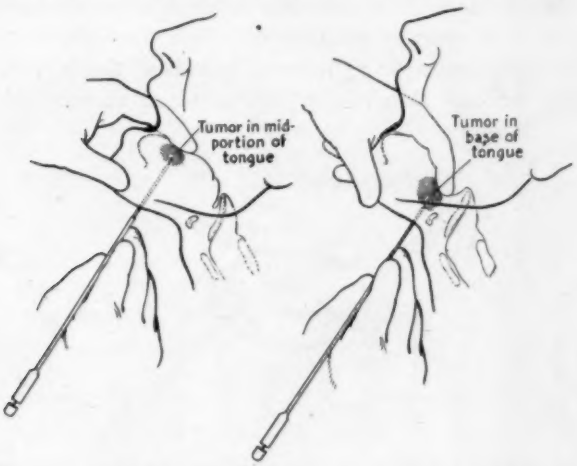

Fig. 10.—For interstitial implantation of tumors of the middle portion or of the base of the tongue, the introduction of infection may be avoided by inserting the implanting trocar through a stab wound in the skin of the submental or suprahyoid region.

late complications frequently ensue. This objection is almost entirely overcome if the open mouth is used as the portal of entry (fig. 11).

An essential factor in peroral roentgen irradiation is the use of metal cylinders attached to the tube holder, which serve to separate the lips and jaws, to retract certain normal intraoral structures in the approach to the tumor, to limit the beam of radiation to the desired volume and area and to insure its correct direction to the lesion. For this purpose we have designed metal cylinders of various diameters (2.5, 3, 3.5, 4, 4.5 and 5 cm.) and with the ends variously shaped. All are made to fit into a master cylinder in order to be readily interchangeable. A detailed description of this technic and the necessary apparatus has been published in a previous report.[28] For the average tumor in the middle

28. Martin, H. E.: Peroral X-Radiation in the Treatment of Intraoral Cancer, Radiology **28**:527, 1937.

third of the lateral border of the tongue, the patient draws the tongue partly out and to one side, and the cylinder is brought down between the lips and the gums and centered directly over the tumor (fig. 11). With daily treatments single doses of 300 to 400 r are given over a period of about three weeks for a total of 5,000 to 8,000 r, depending on the size of the portal, the thickness of the lesion and the dose of supplementary radon seeds. These factors of dosage must remain somewhat empiric and are selected for the individual case on the basis of past experience.

When a tumor on the tip of the tongue is irradiated, the tongue may be protruded from the mouth over a lead plate in which a notch has been cut to fit around the root of the tongue. The beam of roentgen

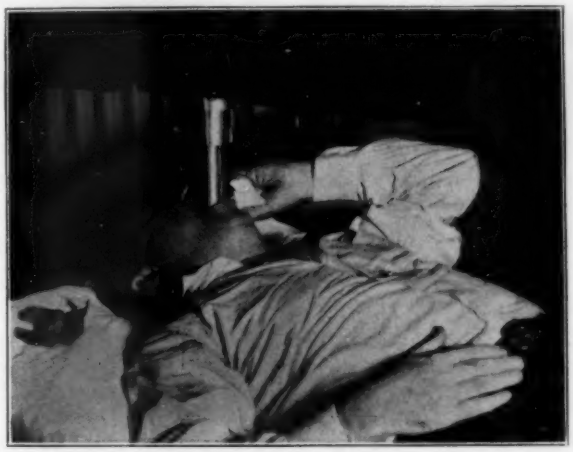

Fig. 11.—Lesions of the anterior two thirds of the tongue may be treated by roentgen radiation given through the open mouth. The patient protrudes and holds the tongue so that the lesion is properly positioned. Cylinders of various diameters are used to obtain the desired size of field. An electrically lighted periscope is used as a final check on the accuracy of the setup.

rays is then delivered to the tumor on the tip of the tongue obliquely downward and backward, and no normal tissues are irradiated except an unavoidable area through the notch into the root of the tongue. Either high or low voltage roentgen radiation may be used. If the depth of the tumor is several centimeters, the more highly filtered roentgen radiation is advisable. Since the tumor is on the surface, the target-skin distance should be reduced (30 to 35 cm.) so as to intensify the superficial effect. The dosage is somewhat empiric and depends on the site of the portal and the intended size of the subsequent complementary dose of radon seeds.

Radon Gold Seeds ("Overdosage") Followed in Five to Ten Days by Partial Glossectomy.—A combination of a massive dose of interstitial radiation followed within five to ten days by local removal of the tumor is a method formerly widely employed in our clinic for the treatment of many bulky lingual cancers. Its indications were based on the fact that many of these larger lesions, if irradiated by adequate doses of interstitial radon, were complicated by local radionecrosis and a long, painful convalescence. The local surgical removal was intended to eliminate the tissues condemned to subsequent radionecrosis. Since the more extended use of fractionated peroral roentgen radiation the incidence of radionecrosis from this cause has been markedly lessened, but partial glossectomy following radiation therapy is still an important technic, especially for the management of recurrences in heavily irradiated tissues.

When this combination of methods is employed, a dose of seeds is selected so as to deliver a desired number of millicuries destroyed within a specified time (five to ten days), after which the local tumor and contained radon are removed by actual cautery. The seeds are so placed in the tumor that they will certainly be removed with it. The dose is therefore termed an "overdosage"; that is, it would be an overdose if the radon were left in place for its total period of decay. If the period between the implantation and cautery removal is short (seven to ten days), one may anticipate the effect of radiation therapy so that the operative procedure is accomplished before the local radiation reaction appears. The rate of decay of radon in from five to fifteen days is given in table 4.

Technic of Glossectomy by Thermocautery.—In certain instances this procedure may be accomplished with local or conduction anesthesia, especially if the lesion lies in the anterior portion, or tip, of the tongue. If the lesion is more extensive or lies in the middle portion or extends to the base of the tongue, short chloroform anesthesia is to be preferred. After induction, the anesthesia is continued by a large nasal catheter inserted down as far as the tip of the epiglottis, and the pharynx proximal to the end of the tube is packed with gauze so as to close the surrounding airway and to prevent the aspiration of blood into the trachea. The tip of the tongue is transfixed by two sutures —one in the portion which is to remain and the other in the segment which is to be removed. The buccal, palatal and labial mucous membranes are next protected by heat-insulative shields (basswood splints shaped to fit). The organ is then drawn out of the mouth and held by sutures. Excision is accomplished by the actual thermocautery, which in our opinion is preferable to any form of endothermy. If the point of the cautery is kept red hot, the cutting is almost as rapid as with endothermy, and capillary oozing is practically nonexistent; fur-

thermore, since deep coagulation is avoided, the cut edges soon take on a healthy granular appearance, with more rapid healing. If the lateral half of the tongue is to be excised, a portion of the tip of the half which remains should be removed by an oblique incision (fig. 12).

Assisted by traction on the transfixed sutures, the line of incision is kept under tension. After division of the free portion of the tip,

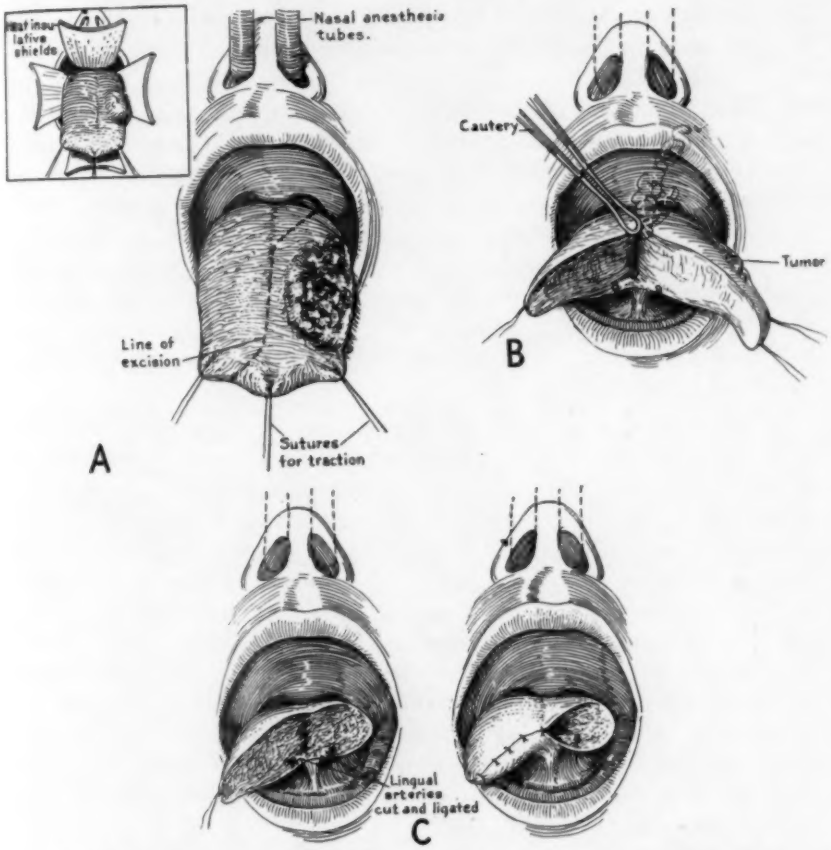

Fig. 12.—Partial glossectomy. *A*, the tongue is drawn out of the mouth and held by sutures. The cheeks and the mucous membrane of the lips are protected by heat-insulative shields of wood. *B*, with use of lateral traction the excision is accomplished by the red-hot point of a thin-bladed cautery. *C*, the cut ends of the lingual arteries are ligated, and the anterior portion of the wound is loosely closed by sutures.

traction is applied in an upward direction and a horizontal cut is made with the cautery in the floor of the mouth, severing the genioglossus and hyoglossus muscles and proceeding backward into the intrinsic musculature, if necessary, to the valleculae, depending on the extent

and depth of the intended excision. The smaller arteries are clamped as they are cut. Suction rather than sponging is to be preferred to keep the operative field reasonably clear of blood as well as of smoke. Marked hemorrhage is not to be feared until one exposes the lingual artery, which enters the under surface of the muscular body of the tongue about opposite the first molar. As the incision progresses, the lingual artery is readily recognized as it appears in the depths of the wound, and at this point it may be grasped by a hemostat and severed. If it is severed without first being seen, the bleeding end is readily grasped by a hemostat and ligated.

The excision may extend backward into the valleculae if necessary, and by this cautery technic no particular difficulty is experienced from hemorrhage. Constant attention must be paid to the proper protection of the lips, cheeks, jaws and palate by heat-insulative shields; otherwise, a blistering of these mucous membrane surfaces may be caused both by contact and by radiant heat. The severed end of the lingual artery is always tied with a suture ligature, and it is usually necessary to tie three or four smaller bleeding points, but the total amount of blood lost should be small. The technic of ligation of these vessels will be described presently.

Treatment of Cancer of the Base of the Tongue.—This anatomic form of the disease, in our opinion, should be considered inoperable in all cases, not only because of the comparative inaccessibilty of this region but because of the highly malignant, rapidly growing, widely metastasizing and radiosensitive nature of these tumors. Cancer of the base of the tongue resembles pharyngeal cancer in many of its clinical features as well as in its favorable response to fractionated external roentgen irradiation. It is, however, neither necessary nor advisable to depend entirely on roentgen irradiation for these tumors, since the base of the tongue tolerates moderate doses of interstitial radiation without difficulty. A combination of external and interstitial irradiation is indicated in practically all such cases, in our opinion. The external irradiation is given first over a period of two to three weeks and followed immediately by supplementary use of radon seeds.

The protracted roentgen irradiation is usually given through the skin of the neck, since the open mouth cannot be satisfactorily employed as a portal of entry to irradiate the base of the tongue. The position of the exact center of the tumor is marked on the skin of the neck after careful inspection by a throat mirror and by digital palpation. With the jaws closed, the base of the tongue and the tumor will be found to lie a little below and anterior to the angle of the jaw. The location of the exact center of the portal will vary only about 2 cm. from the angle of the jaw, no matter what the size and position of the tumor at the base of the tongue, but these short distances are nevertheless of great importance.

In order to conserve the local and general tolerance, portals much larger than 7 to 8 cm. in diameter should not be used unless indicated by the unusual size and extent of the tumor. Portals with a diameter less than 7 cm. are difficult to localize and maintain in place over deep-seated tumors. For the average growth at the base of the tongue 2 to 4 cm. in diameter, using two lateral portals of 7 cm. diameter, one may administer a series of daily roentgen treatments of about 350 r to each side for a total dose of about 3,500 r times 2, and immediately on the completion of this roentgen irradiation insert a supplementary dose of radon seeds to deliver about 5 to 6 skin erythema doses (S. E. D.) (table 4) into the tumor by the technic already described. The strength of the individual seeds should not be above 2 millicuries. If necessary, total doses of 16 to 20 millicuries properly distributed are well tolerated in this region after doses of protracted roentgen irradiation.

Since metastases from the base of the tongue most commonly occur first in the carotid bulb nodes, it is often possible by a slight tilting of the beam to include both these nodes and the primary lesion in the primary beam. The treatment of cervical nodes will be discussed further under a separate heading.

Variations in Technic for Treatment of the Primary Lesion in Cancer of the Tongue.—Occasionally cancer of the tongue will be so radiosensitive that the tumor may disappear early in the course of the peroral roentgen irradiation, and the regression later may become so complete that supplementary treatment by radon seeds may be justifiably omitted. However, in view of the increased safety and the slight disadvantage of a moderate dose of supplementary seeds, such attempts at the control of lingual cancer by external irradiation alone are not advisable, except in rare instances.

Low voltage, lightly filtered roentgen radiation (100 to 120 kilovolts; filter 1 to 2 mm. aluminum) given perorally or to the protruded tongue may be used for very superficial but widespread lesions of the dorsum or of the anterior third of the tongue. The dosage employed is about the same as in the treatment of cancer of the skin. The method has certain disadvantages in that slight errors in technic, especially in exposing the lesion and in shielding the normal structures, are associated with troublesome complications.

As has been previously mentioned, surgical excision alone is seldom indicated for the primary lesion of cancer of the tongue except possibly in those rare cases in which the tumor arises directly in the tip of the tongue and tends to fungate rather than to infiltrate. In these cases, in which the lesions are not the most highly malignant, amputation of the tip of the tongue with a margin of at least 7 to 10 mm. of normal tissue is probably the most expeditious method.

TREATMENT OF METASTASES FROM CANCER OF THE TONGUE

The management of cervical metastases is one of the major problems in the treatment of intraoral cancer, and the degree of success in dealing with this complication determines in great part the eventual prognosis. Over 60 per cent of unselected cancers of the tongue metastasize at some time during the course of the disease. Cancer of the tongue produces about 25 per cent of all cancerous cervical metastases. So far as the medical literature is concerned, most of the statistical reports on the treatment of cervical metastases have been based on series of cases of cancer of the lip, an anatomic form of the disease which is obviously not representative of the whole subject because of its lesser degree of malignancy.

For the treatment of cervical metastases, there are available the same methods as those used for the primary lesion, namely, irradiation and operation. It has been our experience that both of these methods are indispensable, and in a general consideration of the special indications for each we wish to avoid so far as is possible the appearance of any partisan preference for one or the other method. Each method may be specifically indicated in certain instances, and a combination of the two is required in a considerable percentage.

From the strictly surgical viewpoint, cancers are usually classified into "operable" and "inoperable"groups, and customarily no onus is attached to surgery for its failure to benefit the "inoperable group." From the standpoint of irradiation, however, there is no equivalent for the term "inoperable." Therefore, when the treatment is by irradiation or a combination of irradiation and surgical therapy, results are calculated on the basis of all tumors treated, and classification into "inoperable" and "operable" groups is of little practical importance. The apparent percentage of cures calculated on operable cancer treated by surgical intervention alone cannot be fairly compared with the results in all cases of treatment by irradiation and/or surgical intervention.

Limitations of Neck Dissection.—The time honored method for the management of cervical metastases is neck dissection, and this procedure still ranks high under certain limited conditions. In cases of lingual cancer we have found it to have a very narrow range of applicability, for the following reasons: Thirty-five per cent of all cancers of the tongue present metastases on admission. The treatment of the primary lesion alone—either by irradiation or by a surgical procedure—is a major procedure accompanied by marked local complications from which complete recovery cannot be expected for a period of several weeks. Neck dissection is also a major surgical procedure with a definite mortality. We have always believed that aggressive treatment of the primary lesion (either by a surgical procedure or by irradiation) cannot be accompanied or immediately followed by such a procedure as neck

dissection without an undue risk of serious complications or immediate mortality. If, for this reason, the neck dissection is deferred until the primary lesion of the tongue is healed, it will in many cases be too late. We therefore feel that if metastases are present on the patients admission to the hospital there can be little question as to the contraindications for neck dissection.

Should cervical metastases from cancer of the tongue occur immediately after the healing of the primary lesion and therefore early in the course of the disease, an analysis of the clinical course in a large series of cases will reveal that such metastases are very apt to be bilateral or soon to involve widely separated or outlying areas of the neck. Neck dissection in such instances would therefore probably have to be bilateral and extensive within a short period—a condition surely not favorable to a high percentage of cures. There are other factors, such as the advanced age and poor general condition of the patient, which constitute definite contraindications to neck dissection for lingual cancer.

Limitations of Radiation Therapy for Cervical Metastases.—Radiation treatment likewise has certain definite contraindications. From the practical standpoint, one may consider problems of which the following example is representative. After treatment of early cancer of the tongue without metastases, there is prompt healing. The patient attends the follow-up clinic very irregularly but remains free of disease for two and one-half to three years, after which time he appears at the clinic with a fairly early, definitely palpable cervical metastasis on the same side as the primary lesion. Since little dependence may be placed on the regularity of his return over a long period for the multiple visits necessary to complete the irradiation of his cervical nodes, neck dissection would obviously be the best solution of the problem, because the procedure could be completed immediately without the risk of fatal neglect or noncooperation. Other contraindications to radiation therapy alone arise when cervical metastases from lingual cancer are large and bulky, with central necrosis and liquefaction. In certain of these cases, the best solution of the problem lies in a neck dissection alone or in a combination of irradiation and surgical intervention. Specific indications for each particular method will be outlined under a description of technic.

Prophylactic Treatment.—As the term is generally understood, prophylactic treatment refers to those procedures applied to the neck for the control of possible metastases which are not palpable or otherwise demonstrable. Strictly speaking, prophylaxis is not the proper term for this form of treatment, since it is intended not to prevent metastases but to control impalpable metastases which may be present. Such treatment may be either surgical or radiologic.

In the management of intraoral cancer at the Memorial Hospital, such prophylactic treatment to the neck, either surgical or radiologic, is not

employed for these several reasons. It will be conceded that if impalpable metastases are present in lymph nodes or elsewhere their treatment by irradiation or surgical intervention, to be effective, must be just as intensive as if the metastases were palpable and obviously present. As ordinarily advised and given, prophylactic irradiation consists of 1 to 2 skin erythema doses to both sides of the neck or other lymph node-bearing areas of the body. In our experience, such small doses as 1 to 2 skin erythema doses have never been observed (or at least reported) to sterilize a proved focus of epidermoid carcinoma or adenocarcinoma. Why, then, should such a dose be assumed to be capable of sterilizing an impalpable focus of cancer, the actual existence of which cannot be proved, simply because an individual patient survives and does not subsequently have metastases? The argument that by such irradiation any impalpable tumor cell may be partly devitalized is unacceptable, since partial devitalization of curable cancer is not sufficient. Cancer partly devitalized by irradiation to the point of partial necrosis may pursue just as malignant a course as untreated cancer.

The administration of cancer-lethal doses (5 to 8 skin erythema doses) to the entire potential node-bearing area of the neck would, in our opinion, be dangerous and unjustifiable, but this amount would be necessary to be of any possible benefit. Cancer-lethal doses, in order to be tolerated, must be limited to relatively small areas of the body. The actual volume and area occupied by curable palpable metastases are relatively small, and on this condition only may cancer-lethal doses be successfully given for palpable cancer in these areas. It is reasonable, therefore, to limit the application of radiation to cervical metastases according to this principle.

The greatest strength of the argument for prophylactic irradiation of the neck lies in the fact that its efficacy cannot be easily disproved. Reports of end results are frequently cited in support of its alleged benefits, but since the actual presence of the initial metastatic involvement remains extremely doubtful, the argument is purely negative and entirely unconvincing to the critical observer.

The lack of justification for any form of prophylactic treatment of the neck, especially radical neck dissection, can be further proved by statistical analyses. It is obvious that prophylactic treatment to the neck, even though efficacious, can be of no ultimate value unless the primary lesion is permanently controlled. Since this is true, it is highly significant that in our analysis of a series of 118 cases of cancer of the tongue limited by selection of those in which the patients were admitted without palpable nodes and in which the primary lesions were eventually permanently controlled, only 22 per cent of patients later had cervical metastases. In the final analysis, in only the latter 22 per cent would any form of treatment to the neck, prophylactic or otherwise, be of curative

value. It is also obvious that if prophylactic neck dissection had been performed in the whole group of 118 cases, they would have been of value in only 26 of these cases (1 in 5), while 92 useless operations would have been done (4 in 5), with a definite operative mortality. Under the higher reported mortality rates (10 per cent), about 12 of these patients would have died of postoperative complications. On the other hand, if neck dissections were omitted until nodes became palpable, only one fifth as many operations would be necessary.

The practical application of these principles may be expressed by the following general rules for the management of cervical metastases.

1. If no palpable metastases are present, no treatment of any kind should be given.

2. If palpably and clinically involved nodes are present, one should limit treatment by irradiation to the individual nodes themselves, sparing

TABLE 5.—*Methods Used at the Memorial Hospital for the Treatment of Cervical Metastases*

1. Protracted external irradiation through small portals followed by implantation of radon seeds. This method is the most generally useful for treatment of all cervical metastatic cancer
2. Radical neck dissection. This method has a limited application but is very useful when indicated
3. Radon seeds alone. This method is indicated only for very small or isolated nodes
4. External irradiation alone. This method is useful only in very radiosensitive tumors
5. Variations and combination methods:
   - A. Surgical exposure and implantation of radon seeds
   - B. Implantation of radon seeds in heavy dosage followed in 10 to 15 days by surgical excision
   - C. Surgical excision followed by radon seed implantation for an irremovable residuum

outlying clinically uninvolved areas and administering local radiation treatment to such outlying areas only if they later become involved.

3. If the treatment is to be neck dissection, the extent of this procedure is determined mainly by the anatomic form of the disease. Since neck dissection can be performed only once in a given area, it must therefore be complete within a given zone.

The methods available for the treatment of cervical metastases at the Memorial Hospital are outlined in table 5 in the order of their usefulness of application.

Protracted External Irradiation Followed by Implantation of Radon Seeds (Method 1).—This method is probably the most useful and the most generally applicable to cervical metastases from the various anatomic varieties of intraoral cancer. In general, the purpose of this method is to confine the radiation to the immediate vicinity of the node in order to conserve as much as possible the integrity of the adjacent tumor bed and the general tolerance of the patient. External and inter-

stitial radiation are combined so as to derive the greatest possible benefit from a cumulation of their desirable effects. Their respective undesirable effects differ somewhat and are therefore not cumulative to the same degree. The main disadvantage of the method is that it is time consuming (three to four weeks) and, therefore, one of the simpler and less time-consuming methods may occasionally be preferable. Aspiration biopsy of the enlarged node should always be performed for purposes of record.

To localize the external irradiation, small circular portals (3 to 5 cm. in diameter) are applied to each separate node, and depending on the size of the portal a total of 4,000 to 8,000 r or even more is given by daily divided doses over a period of two to three weeks. Immediately on the completion of this external dose, radon seeds in a tissue dose of 5 to 10 skin erythema doses (table 4) are implanted either through puncture wounds in the skin or after surgical exposure of the outer surface

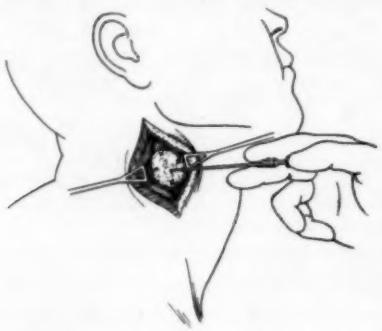

Fig. 13.—Accuracy in implanting radon seeds in metastatic cervical nodes is favored by surgical exposure of the outer surface of the node.

of the node, in which case the cutaneous reaction to the roentgen rays is anticipated by performing the surgical exposure after about two weeks of irradiation. If the tissues are handled gently, an already blistered cutaneous surface may be painted with iodine and incised for exposure of the node, with prompt healing of the wound. With experience, the surgical handling of irradiated tissues, either early or late, presents only moderate difficulty.

This conservative method of treatment, when applied only to the immediate area of the clinically cancerous node, makes possible its repetition in other areas should they be subsequently involved. Treatment of the necessary cancer-lethal intensity would not be tolerated if applied diffusely throughout the entire cervical region where metastases might subsequently appear.

Radical Neck Dissection (Method 2).—The indications for neck dissection have already been discussed in some detail and will not be

repeated at this point, except to say that in cases of cancer of the tongue this procedure will be most useful if limited to those cases which conform to the following conditions:

1. Metastatic cancer should be palpably demonstrable in the neck.
2. The primary lesion should be healed and show no recurrence.
3. The primary lesion should neither have involved nor crossed the midline.
4. The metastases should be operable from the standpoint of their location and their mobility in the tumor bed.
5. The metastases should be unilateral and on the same side as the primary lesion.
6. The patient's general condition should be such as to withstand operation.

The foregoing conditions under which neck dissection is permissible may seem rather rigid. However, it will be found, we believe, that few permanent cures of metastatic cancer of the tongue will be accomplished by neck dissection in cases which do not conform to the aforementioned conditions. If the case does not so conform, we believe that radiation methods offer a much greater chance of cure.

We favor local rather than general anesthesia in all cases of neck dissection, even though the patient may insist on general anesthesia. The highest mortality due to neck dissections (11 per cent) is reported from those clinics where general anesthesia is used as a routine procedure.

As compared to some other forms of intraoral cancer, the area of neck dissection for cancer of the tongue must be much more extensive. The operative area must extend from the midline of the neck (or beyond) to the anterior border of the trapezius muscle—from the inferior edge of the mandible and mastoid process to the clavicle.

The most useful types of incision, in our experience, are those illustrated in figure 14. Superficially, the plane of dissection should lie on the inner surface of the platysma myoides muscle and at about the same depth in the subcutaneous fat beyond the borders of this muscle. In superficial dissection the removal of the platysma myoides muscle probably does not increase the chance of cure, since the presence of metastatic cancer in the superficial lymphatics occurs only by a retrograde spread relatively late, when the disease ipso facto is incurable by operation.

In the course of the dissection all lymph node–bearing tissue between the platysma myoides muscle and the deep muscles is removed, including the jugular vein, the sternomastoid and omohyoid muscles and the submaxillary salivary gland. No attempt is made to isolate the eleventh cranial nerve, which is sacrificed. The tip of the parotid salivary gland is cut across.

In closing the wound it should be realized that a great number of lymphatics have been severed and that there will be profuse serous discharge for the first few days. Therefore, several soft rubber tube drains should be inserted.

Implantation of Radon Seeds Alone (Method 3).—This method of treatment may occasionally be indicated for isolated outlying small nodes or small nodes recurring after any form of treatment. In general, this method should be reserved for the smaller masses in which a heavy

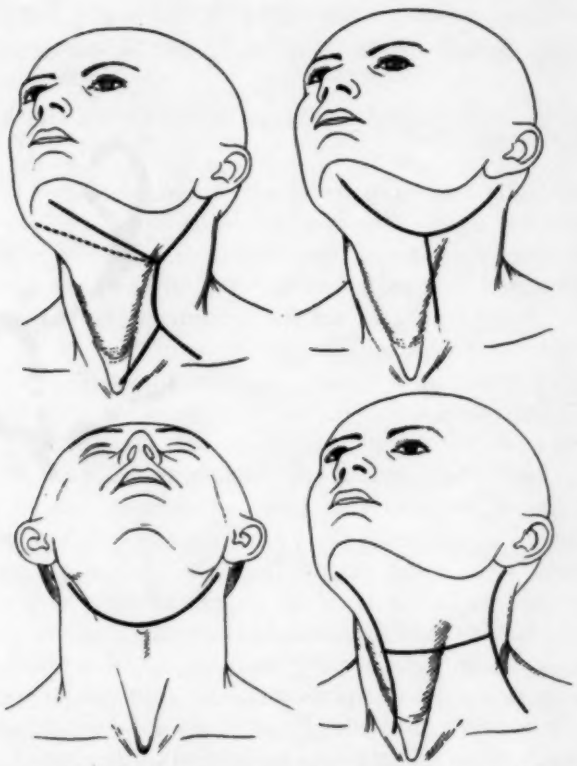

Fig. 14.—The most useful forms of incision for neck dissection.

tissue dose may safely be given in a small volume by a moderate dose of radon seeds. The seeds may be inserted either through the skin or after surgical exposure. The dose depends on the size of the node and should be selected so as to deliver at least 10 skin erythema doses (table 4) or more throughout the mass. The proper geometric arrangement of the seeds is important, and the same rules should be followed as are described for the treatment of the primary lesion.

External Irradiation Alone (Method 4).—This method may be sufficient for metastases from the more anaplastic and highly radiosensitive

growths at the base of the tongue. It often happens that a metastasis in the upper deep cervical chain will lie directly superimposed over a primary lesion at the base of the tongue. Since treatment in such cases is always given first and mainly by external irradiation, the node will occasionally regress promptly and completely at the same time as the primary lesion under external irradiation alone, so that at the end of three to four weeks all evidence of the disease disappears. In these cases, one may occasionally feel justified in giving no other treatment. However, if the node regresses more slowly than the primary lesion or is palpable at the completion of the external irradiation, it is far safer to implant a supplementary dose of seeds, as in method 1.

Variations in Procedure.—Surgical and radiologic procedures may be combined in several ways for cervical metastatic cancer, but we lack space to discuss them in detail here.

COMPLICATIONS

The complications following surgical procedures are apt to be acute and severe but of short duration; those following radiation treatment tend to be of lesser degree (at least in the beginning) but of longer duration.

Pain.—The radiation reaction usually causes no particular discomfort when the tongue is at rest, but there is pain on movement, so that the patient tries to avoid any motion of the tongue, such as that necessary in the act of swallowing. A temporary increase in the salivary secretions and the seromucoid excretions from the tissues involved by the radiation reaction results in distressing salivation. For this complication, nothing gives greater relief than frequent mouth washes with compound solution of sodium borate (Dobell's solution) or copious irrigations of the mouth with a mild solution of sodium bicarbonate and saline solution. If a lesion with deep ulceration or radionecrosis is limited to one nerve distribution, such as the anterior third of the tongue and the adjacent floor of the mouth on one side only, neurolysis of the third division of the fifth cranial nerve by injection of alcohol may be indicated.

Since pain in cancer of the tongue is a symptom which will persist over a period of several weeks, morphine is not suitable except when the prognosis is hopeless and the period of life expectancy does not exceed about two months. If the life expectancy exceeds this period to any great extent, one must take into account such factors as the increasing doses necessitated by addiction, the cost and the possible difficulty in obtaining and administering large quantities of the drug. A form of medication which we have found to be of most service is 10 grains (0.65 Gm.) of acetylsalicylic acid combined with ½ grain (0.03 Gm.)

of codeine, which the patient takes himself at six hour intervals, with the admonition that he is to use as little as possible.

Necrosis.—This complication, while frequent in all bulky irradiated surface cancers, is occasionally seen in the untreated advanced cancer of the tongue. It may also occur in early stages of the disease as a complication following irradiation, but is not due to the lethal effects of radiation alone. Unless infection is introduced, a completely devitalized area of cancer, deeply seated, will usually either be entirely eradicated by absorption or eventually resolve into a nonvascular calcified mass. However, if infection enters, the phenomenon known as radionecrosis accompanied by sloughing of the tissues invariably results. For all practical purposes, radionecrosis does not occur in the absence of infection.

Once initiated, the subsequent extent of this complication is determined by the intensity and extent of the tissue dose of radiation. Therefore, in order to localize the possible radionecrosis as well as other untoward effects of radiation a great deal of attention should be given to the principle of the most efficient manner of irradiation, including the geometric placement of the sources of interstitial radiation and the use of the smallest possible skin portals for external irradiation. Radionecrosis of limited extent may often be dealt with by local conservative measures, such as mouth washes, irrigations, sprays and the daily removal of slough, but in the case of persistent or widespread involvement convalescence is shortened by partial glossectomy, in which one removes the devitalized area with fair margins of viable tissue surrounding it.

Hemorrhage.—This complication seldom occurs except in association with radionecrosis, although it may be caused from actual erosion by the tumor without necrosis. Although hemorrhage is by no means always fatal, in over 10 per cent of our unsuccessfully treated patients death was due to this cause. The blood supply of the tongue is mainly from the lingual artery, whose branches anastomose to some extent in the base of the tongue and in the tonsillar region with branches of the superior thyroid and facial arteries. The lingual artery enters the tongue medial to the hypoglossus muscle and runs forward deep on the under surface of the tongue as the linguae profunda artery. It is the latter branch which is usually responsible for the most severe hemorrhage in cancer of the tongue. The dorsal lingual branch ascends through the lingual substance to supply the base of the opposite side around the foramen caecum. With the exception of this anastomosis and one at the tip of the tongue, the two lingual arteries do not have any marked communication across the midline of the tongue—a point of practical value in the control of hemorrhage. In surgical excision or in radionecrosis, it will be found that severe or dangerous hemorrhage sel-

dom occurs except from erosion of the linguae profunda artery. Hemorrhage from the base of the tongue is seldom profuse except when the erosion is deep enough to involve the main branch of the lingual or the facial artery. The lack of any elaborate anastomosis across the midline makes it unnecessary to ligate the arteries of both sides except when the necrosis or the operative procedure extends well across the midline.

Hemorrhage from an eroded lingual artery may be profuse, and death may occur from exsanguination within a few minutes. In the average case, however, the first hemorrhage is not apt to be fatal. In radionecrosis of the floor of the mouth, the spurting end of the vessel is not easily grasped directly, and tamponage is much more effective. A folded piece of gauze is pressed into the floor of the mouth and held by the finger. Immediate steps must be taken to clear the pharynx of blood, which may otherwise be aspirated and result in pulmonary complications.

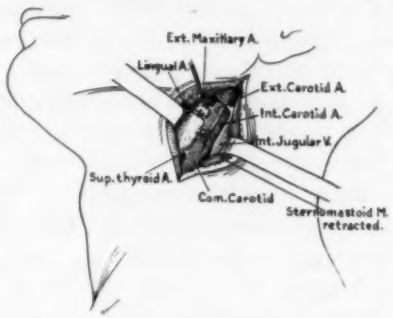

Fig. 15.—In hemorrhage from the tongue or the floor of the mouth, the lingual artery and usually the facial and external carotid arteries may be conveniently exposed and ligated by an incision along the upper anterior border of the sternomastoid muscle. It is advisable to cut the lingual artery between ligatures in all cases. The likelihood of recanalization is also reduced if ligatures of fine steel wire are used.

In all hemorrhages from cancer of the tongue, prompt ligation of the vessels of the neck is indicated.

Technic of Arterial Ligation for Hemorrhage from the Tongue.—The blood supply of the anterior portion of the tongue is derived from the lingual artery, with the addition of the tonsillar branch of the facial artery (external maxillary) which in part supplies the base. It is usually recommended in surgical texts that all of these vessels be approached by an incision through the submaxillary triangle, but we believe that they are best exposed for ligation at the bifurcation of the common carotid artery, which lies under the anterior edge of the sternomastoid muscle, a little below the level of the angle of the jaw. The latter approach gives the most direct access to these several branches as well as to the

external carotid artery itself, which should often also be ligated. We have described the technic of this operation in detail elsewhere. Should the hemorrhage originate from a centrally situated lesion, bilateral ligations may be performed, with an interval of five to ten days between operations if possible. The elaborate anastomosis of the terminal and deep branches of the thyroid plexus are such that no fear need be entertained for the vascular nutrition of the structures of the oral cavity or pharynx after these bilateral ligations of the external carotid artery.

Sepsis.—This complication is inevitable in some degree in practically all cases of intraoral cancer under any method of treatment. Its significance in the early attempts at resection of the tongue was discussed at great length by Butlin, especially in the first edition of his "Diseases of the Tongue."[4b] The most useful measures for combating sepsis have already been described under the hygienic care of the mouth.

Pulmonary Complications.—In the presence of advanced and complicated oral cancer, when the hypopharynx is examined with a mirror, a quantity of fluid, consisting of saliva, mucus and pus, will usually be found filling the piriform sinuses. Since swallowing is painful, these accumulated fluids tend to spill over into the larynx through the interarytenoid space and to be aspired into the trachea. Bronchopneumonia (and, occasionally, pulmonary abscess) may result—the most frequently mentioned cause of death from the surgically treated lesions. The incidence of these, as well as of most other complications, may be greatly reduced by careful attention to the details of nursing care, especially with reference to oral hygiene.

Osteomyelitis.—With all forms of intraoral cancer treated by massive doses of roentgen therapy, osteomyelitis is an occasional complication, and its inception depends largely on the diffuse irradiation of the bone, after which any exposure of its surface, either by necrosis of the overlying tissues or by extraction of teeth, is apt to be followed by infection of the bone. Watson and Scarborough,[29] of our clinic, have described this complication in more detail in relation to intraoral cancer. Osteomyelitis developed in about 10 per cent of patients in our series with lingual cancer. If not exposed to infection from the outside, such avascular bone may remain and function without incident in the same manner as a dead bone graft or an ivory peg. However, this devitalized bone will behave as will any foreign body if infection is introduced; that is, an abscess is formed in this area and healing will take place only after sequestration and extrusion of the avascular bone.

There are several ways in which the incidence of osteomyelitis may be reduced. The first is by the use of peroral portals, such as those which we have already described, to avoid diffuse and unnecessary irradi-

29. Watson, W. L., and Scarborough, J. E.: Osteoradionecrosis in Intraoral Cancer, Am. J. Roentgenol. **40**:524, 1938.

ation of the jaws. The second method is to avoid as much as possible the extraction of teeth at any time before, during or after local irradiation. The third is to make the interstitial doses as small and as effective as possible. With the firm conviction that the extraction of teeth is apt to be followed by serious complications in these cases, we use every reasonable alternative such as cutting off teeth at the gum level, killing the nerves and filling the root canals.

Once established, radio-osteomyelitis of the jaw should be treated conservatively, at least until the probable extent of the sequestration can be determined. The complication is less serious in the upper jaw than in the lower. In the latter, the arterial supply is from an end artery (inferior dental), and little assistance can be expected from anastomosis. In the upper jaw osteomyelitis tends to localize rather quickly; in the lower jaw it tends to be progressive. Partial resection of the mandible may be necessary in cases of aggravated lesions.

Edema of the Hypopharynx and of the Glottis.—When in the late stages of lingual cancer a lesion at the base accompanied by widespread cervical metastases has been heavily treated with roentgen radiation through large portals, edema of the epiglottis and of the arytenoids frequently occurs, with concurrent dyspnea and dysphagia. The dysphagia may require the insertion of a nasal feeding catheter. The dyspnea may necessitate a tracheotomy, and in such a case, the incision should be as short and placed as low as possible.

PROGNOSIS

Except in the earliest stages, in which the tumor is small and situated on the edge of the anterior half of the tongue, the prognosis of cancer of the tongue is bad, and the only opportunity for cure lies in treatment by those especially trained. In the fatal cases in our series, the average duration of life from the first symptom to death was twelve months. Excluding immediate postoperative deaths, the duration varied between two months and seven years. Of all the unsuccessfully treated patients, 60 per cent died within one year after the beginning of treatment.

It will be noted in table 6 that the prognosis is best (47 per cent) under the age of 40 and that the cure rate progressively falls with advancing age to the poorest (19 per cent) over the age of 60. It should be realized, however, that our series does not necessarily represent the natural course of the disease, but rather the clinical course under aggressive treatment.

Sex.—Our figures indicate that the chance of cure of cancer of the tongue in the female is almost 30 per cent better than in the male. The influence of sex on the prognosis of pharyngeal cancer treated by irradiation has already been noted by other observers. We believe that this

better prognosis is due largely to the fact that cancer of any given histologic or anatomic form is generally more radiosensitive in the female than in the male.

Stage of the Disease.—In table 6 we have arbitrarily classified the lesions into three groups—"operable," "borderline" and "inoperable"—for the purpose of comparing our results and prognosis with other published statistics. In our clinic, such a classification has little influence

TABLE 6.—*Factors Influencing the Five Year Cure Rate in 530* Cases of Lingual Cancer Observed at the Memorial Hospital from 1927 to 1934*

	Total Number of Cases	Number of Five Year Cures	Per Cent of Five Year Cures
Age in years:			
Below 40	32	15	47
41 to 50	87	25	29
51 to 60	186	42	23
Over 60	225	42	19
	530		
Sex:			
Males	457	101	22
Females	73	23	31
	530		
Stage of disease:			
"Operable"	141	80	57
"Borderline"	58	21	36
"Inoperable"	331	23	7
	530		
Metastases:			
None at any time	191	85	45
None on admission	320	108	34
Developed after admission	129	23	18
Some time during course	339	39	12
Present on admission	210	16	8
Histopathologic structure:			
Epidermoid carcinoma grade I	71	33	46
Epidermoid carcinoma grade II	318	64	20
Epidermoid carcinoma grade III	42	2	5
Adenocarcinoma	7	1	14
Transitional cell carcinoma	16	3	19
Lymphoepithelioma	3	1	33
Not classified	73	20	27
Associated leukoplakia	159	52	33
Associated syphilis	122	24	20

* The discrepancy between this figure (530) and the grand total (556 cases) is due to the fact that in the earlier series (1927-1931) the calculations were made on the entire group, while in the second series (1931-1934) the "indeterminate cases" were excluded.

in the selection of the treatment method; that is to say, the fact that a cancer is classified as "operable" does not signify that surgical treatment is the preferable method. In any case, such a classification must be rather arbitrary, since the opinions of individual clinicians must differ considerably.

The operability in the given case must be determined not only on the anatomic features of the primary lesion but on the operability of any cervical nodes and on the general condition of the patient. If radiation were not available, we believe that the tumors comprising the aforementioned operable group would be those selected for attempts at surgical cure in the average surgical clinic. Our five year cure rate in this

group treated by irradiation, surgical intervention or combinations of the two was 57 per cent, a figure which, so far as we have been able to determine, has not been equaled in any purely surgical statistics, even by the most careful selection of cases.

The "inoperable" group includes all tumors of the base or posterior third of the tongue, all lesions which deeply invade the floor of the mouth and anterior tonsillar pillar and those with which it would be impossible to remove a margin of at least 1 to 1.5 cm. of palpably uninvolved normal tissue. Patients with surgically inoperable cervical nodes, bilateral nodes on the side of the neck opposite the primary lesion, would also be included in this class, as well as those patients whose age and general condition would be contraindications to operation. The lesions which we have classified as inoperable and which make up 62 per cent of the total would probably not be mentioned, or at least not included in the calculation of end results, in any strictly surgical report. Our cure rate in this advanced group was only about 7 per cent. In interpreting the reasons for this low cure rate, it must be considered that the inoperable group includes all advanced and recurrent hopeless lesions, none of which has been excluded for this reason alone.

The "borderline" group is made up of those tumors in which the findings are not definite enough to permit of classification in either the frankly operable or the frankly inoperable group. The disposition of this group would depend largely on the courage and technical ability of the surgeon. The prudent surgeon would probably consider most of these tumors inoperable. Our cure rate in this small group, treated by a combination method, was 36 per cent, which is considerably better than the average for the whole. The mean cure rate in the whole series is determined to a considerable extent by the low cure rate in the inoperable group.

In Lane-Claypon's [2] compiled tables listing the postoperative survivals reported by various surgeons, there is included in each of the titles the phrase "all stages of the disease." The fallacy of such a heading is immediately apparent. Since all of the patients were treated surgically, the reports obviously cannot include all stages of the disease, but only the operable and therefore early lesions.

Position of the Growth.—The chance of cure of a tumor at the base of the tongue is only about one third that of a lesion in the anterior portion. This relatively poor prognosis is due mainly to the fact that cancer of the base of the tongue is practically never diagnosed early. Another factor in prognosis is a higher percentage of anaplastic and histologically malignant growths at the base of the tongue than in the anterior two-thirds.

Little difference is found in the prognosis of tumors variously situated in the anterior two thirds of the tongue. The least malignant

variety of lingual cancer is that which arises directly at the tip to form a fungating, papillary, only slightly infiltrating growth which tends to metastasize rather late in the course of the disease, if at all. This relatively good prognosis is counterbalanced by the more malignant character of those lesions arising on the lateral edges or under surfaces of the anterior third of the tongue. Such growths tend to be highly malignant, to infiltrate the floor of the mouth and to metastasize early in the course of the disease. Growths of the middle third (the most frequent site) carry about an average prognosis. Lesions arising on the dorsum are usually associated with long-standing and widespread leukoplakia, and, although these lesions are not in themselves of the most malignant character, they tend to be multiple or successive, since the mucous membrane of the whole dorsum of the tongue has usually undergone marked precancerous changes.

Metastases.—The significance of this complication in the prognosis depends to a great extent on whether the metastatic nodes are present on admission (8 per cent cure rate in our series) or whether they develop after admission (18 per cent cure rate—only a little less than the average for the whole group). As we have previously mentioned, the net cure rate for the whole group (25 per cent) is markedly influenced by the low cure rate (8 per cent) which is obtained in the advanced group with metastases on admission. In the group in which no metastases were present (either on admission or at any time during the course of the disease), the cure rate was 45 per cent. This high figure is obviously due to the fact that this group was not only early but also included the less malignant varieties of lingual cancer.

Histopathologic Structure.—Different portions of a given neoplasm may show different histologic structures. For instance, we have frequently observed intraoral cancers in which the first biopsy showed an epidermoid or squamous carcinoma grade 1 while later biopsies of the same lesion or of a metastasis revealed a different histologic picture, that is, squamous carcinoma grade 2 or 3. Similarly, the first biopsy of an untreated lesion may show a highly anaplastic tumor, but after incomplete regression under heavy irradiation a second biopsy may show a low grade radioresistant tumor in the residuum. In general, the low grade tumors follow a more benign course than do the anaplastic growths. Wide departures from the expected clinical courses are frequently found, and too much reliance should not be placed on tumor grading in the individual case unless supported by other clinical findings.

END RESULTS

A survey of the literature for reported end results in the treatment of cancer of the tongue reveals very few data suitable for comparison.

We have found few based on unselected clinical material.[30] The most common fault with reported end results in cases of cancer of the tongue lies in the fact that the percentage of cures has been calculated only from lesions operated on (operable tumors). This practice began when surgical treatment was the one method and when the percentage of operable patients applying for treatment was probably even smaller than it is at the present time. Though permissible in the time of Butlin, this method is entirely inadequate today. Inoperability of cancer is no longer synonymous with incurability, and the general mortality or curability of cancer or of any given disease cannot be calculated from the cure rates obtained in minority cases.

It must be realized further that an indiscriminate collection of lingual cancers cannot be divided readily into two distinct clinical groups—the operable and the inoperable. There must always be a large portion of borderline tumors, the exact classification of which would depend to a large extent on the experience and the courage of the individual surgeon. We have attempted to survey all of the literature of the past twenty years on cancer of the tongue in order to obtain end result data for comparison. Practically all of the reports give the end results only in highly selected groups, usually consisting of patients operated on. We have considered suitable only those reports which were made on groups of cases which were unselected and in which the period of observation of the whole group was five years or more.[31]

The standard form used in our clinic for reporting end results is set down in table 7. It should be noted that all patients, in any and all stages of the disease, are accepted for record and are included in our calculations if they are able and willing to return for such treatment, palliation or observation as we deem advisable. No patient is excluded because of the advanced stage of the disease. Invariably a small number of patients (1 to 3 per cent) disappear after only one or two visits, possibly to take treatment elsewhere. These "clinic shoppers" and patients seen only once for purposes of consultation are not included in our end result calculations. A second type of patient excluded from our calculations is the nonambulatory patient (also 1 to 2 per cent) who is unable for one reason or another to return for treatment or palliation.

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30. Blair, Brown and Byars (Our Responsibility Toward Oral Cancer, Ann. Surg. **106**:568, 1937), after reviewing about 400 papers on cancer of the tongue, reported finding not a single one which gave satisfactory data for calculation of a true end result figure. Curiously enough, they then fell into the same error themselves by reporting only end results in 40 cases in which they had operated, rather than in the whole group from which the 40 cases of operable growths were selected.

31. Berven.[21] Roux-Berger.[22] Welch and Nathanson.[26f]

Several biostatisticians whom we have consulted have agreed that if the untraced patients who are free from disease constitute less than 10 per cent of the total, they may fairly be classified as indeterminate for statistical purposes. Untraced patients who still had cancer when last seen should be counted as failures. These inconclusive cases, in which (1) the patients have died of other causes without recurrence and (2) the patients have been lost track of without recurrence, constitute the indeterminate group, which should properly be subtracted from the total before the net end result is calculated. Any calculation made without this subtraction is inaccurate and does not represent what may be accomplished in the treatment of a given disease.

TABLE 7.—*Five Year End Results in Cases of Cancer of the Tongue Observed at the Memorial Hospital from 1927 to 1934*

This series consists of the cases of all patients with histologically proved cancer of the tongue, both early and advanced, admitted during the specified period. Only those patients are excluded who, for any reason, were unable to return for treatment, palliation and observation in the outpatient department, and those who were lost track of within the first month after no more than one or two visits ("clinic shoppers").

Total number of patients		556
Indeterminate group:		
Dead as a result of other causes and without recurrence	53	
Lost track of without recurrence	5	
Total number of indeterminate results		58
Determinate group: Total number minus those of indeterminate group		498
Failures:		
Dead as a result of cancer	368	
Lost track of with disease (probably dead)	2	
Living with recurrence	4	
Total number of failures in treatment		374
Successful results: Free from disease after five years or more		124
Five year end results: Successful results divided by determinate group (124/498)		25%

Calculated by the foregoing standards, the end results in the Head and Neck Service at the Memorial Hospital in the treatment of cancer of the tongue from 1927 to 1934 are given in table 7.

SUMMARY AND CONCLUSIONS

A series of 556 consecutive unselected cases of cancer of the tongue have been subjected to intensive clinical analysis and report. The past and present day methods of the treatment of lingual cancer are discussed, and a description is given of the methods now in use at the Memorial Hospital. The prognosis in this disease has been studied by the analysis of five year survival rates in various selected minority groups. A net five year cure rate of 25 per cent has been obtained on the group as a whole.

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PERFORATION AS A COMPLICATION OF GASTRIC CARCINOMA

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Perusal of the medical literature impresses one with the infrequency of references to perforation as a complication of gastric carcinoma. However, admission to the hospital of 2 patients with acute gastric perforation within one week was considered to be of sufficient interest to warrant presentation of the cases, with a review of those observed in the St. Louis City Hospital during the past ten years. Perforated peptic ulcers of the stomach present a more familiar surgical emergency, occurring in approximately 15 per cent of cases.[1] Preoperatively, differentiation between the types of perforation may be difficult if not impossible, because little if any time is afforded the various differential procedures, such as analysis of the gastric contents and complete roentgen studies.

The most comprehensive of the reports in the recent literature is that of McNealy and Hedin,[2] who reviewed 133 cases of perforation of gastric carcinoma. The incidence of perforation in this series was 4 per cent. They classified the lesions into the classic and the obscure type, the former presenting the classic symptoms of sudden onset of pain and abdominal rigidity and the latter being more benign in its course, with no evidence of generalized peritonitis. Numerically the two groups were about equal.

Other reviews are those of Aird,[3] Allen[4] and Friedenwald and McGlannon.[5] Aird summarized the literature, presented a case from his own practice, 7 cases from the Royal Infirmary of Edinburgh, Scotland, and 71 cases from the literature and then concluded that either

1. Da Costa, J. C.: Modern Surgery, ed. 10, Philadelphia, W. B. Saunders Company, 1931, p. 885.

2. McNealy, R. W., and Hedin, R. F.: Perforation in Gastric Carcinoma, Surg., Gynec. & Obst. **67**:818, 1938.

3. Aird, I.: Perforation of Carcinoma of the Stomach into the General Peritoneal Cavity, Brit. J. Surg. **22**:545, 1935.

4. Allen, A. W.: Carcinoma of the Stomach with Perforation and Metastasis to the Liver, Regional Lymph Nodes and Pelvis, New England J. Med. **214**:647, 1936.

5. Friedenwald, J., and McGlannon, A.: Perforation in Carcinoma of the Stomach, Am. J. M. Sc. **157**:1, 1919.

the complication is most uncommon or it is improperly diagnosed. He divided the 79 lesions into four clinical types, the first two of which represent two thirds of the reported lesions and correspond with the classic type of McNealy and Hedin.

During the ten year period 1930 to 1939 inclusive, 247 patients with gastric carcinoma were admitted to the St. Louis City Hospital. This is probably a conservative estimate, for only those whose lesions were diagnosed by physical plus roentgen examination and treated by operation, with biopsy or autopsy, were included. A history and physical examination alone, however suggestive, were not considered to be sufficient evidence for a positive diagnosis. In this series there were 7 cases of acute perforation with the typical picture of acute peritonitis, proved by operation with biopsy and/or autopsy. Obscure cases of chronic or localized perforation were not included because of the difficulty of classification due to the wide variations in symptoms and findings. This means that acute perforation was encountered as a complication in 2.4 per cent of cases of gastric carcinoma.

The average age of the patients in the entire series was 63 years, whereas the average age of those whose lesions perforated was 51 years. Of the total number of patients admitted, 200 were men and 47 were women, a ratio of 4 to 1. All of the perforations occurred in men.

The history and physical findings were typical with all the lesions which were complicated by perforation—pain, commencing as a sudden epigastric crisis and later spreading over the entire abdomen and giving rise to exquisite tenderness, and the classic boardlike rigidity. Roentgenograms taken in 4 cases revealed the presence of free air under the diaphragmatic leaflets in 2. Simple closure of the gastric perforation was undertaken in 5 patients and only 1 of these lived to leave the hospital.

REPORT OF CASES

CASE 1.—E. L., a 67 year old white man, entered the City Hospital on Aug. 28, 1939, complaining of severe epigastric pain which had commenced suddenly about nine hours prior to hospitalization. The pain, which had its onset shortly after the evening meal, was so severe that the patient had to be helped into bed. The pain did not radiate but remained in the epigastrium and about the umbilicus. There were no pains in the shoulders or in the scapulas. The patient vomited three times but noticed no bright red blood or "coffee ground" material in the vomitus. There was elicited a history of indigestion during the preceding five months, with a loss of 20 pounds (9.1 Kg.) in weight during the same period. The indigestion was described as a "stuffy" sensation in the epigastrium, coming on shortly after meals and relieved by baking soda. There was no history of melena. Up to five months previously the patient had been entirely free of any symptoms referable to the gastrointestinal system.

Examination revealed the patient to be rather slender, somewhat emaciated and pale. He appeared to be in moderate shock. The temperature was 101.6 F.; the pulse rate, 116; the respiratory rate, 32, and the blood pressure, 115 systolic and 68 diastolic. The abdomen was boardlike in its rigidity and did not move with respiration. There was rebound tenderness over the entire abdomen, most marked just superior to the umbilicus. It was impossible to palpate the intra-

Fig. 1.—Biopsy specimen taken from the border of the gastric perforation, revealing bundles of muscle tissue between which are seen islands of infiltrating cells. This cellular element is made up for the most part by lymphocytes, but among these are included nests of polyhedral epithelial cells. The nuclei of the latter cells are round, and the cytoplasm is quite clear. No attempt at differentiation is observed (Dr. S. H. Gray, pathologist).

abdominal viscera because of the rigidity. Percussion failed to reveal hepatic tympany, and on auscultation there was no evidence of peristalsis. The heart and lungs were essentially normal; scapular hyperesthesia could not be elicited.

A rectal examination revealed no gross abnormalities. The blood counts on admission were as follows: white cells, 7,000 per cubic millimeter; red cells, 3,780,000 per cubic millimeter, and hemoglobin, 80 per cent. The urine showed no sugar, but there was a trace of albumin. The Kahn reaction of the blood was negative. The value for blood sugar was 86 mg. and that for nonprotein nitrogen 23 mg. per hundred cubic centimeters. A plate of the abdomen with the patient sitting revealed the presence of free air under the left diaphragmatic leaflet.

A diagnosis of generalized peritonitis due to a ruptured gastric ulcer was made, and after adequate parenteral hydration the patient was subjected to an exploratory laparotomy. The abdomen was opened and explored through an upper right rectus muscle-splitting incision. About 1,000 cc. of cloudy fluid was found free in the general peritoneal cavity, extending down as far as the pelvis. There was no fecal odor to this fluid, and a culture was later reported as sterile. The greater omentum covered part of the anterior surface of the stomach, and a large amount of fibrinoplastic exudate had collected about the gastric bed. A hard, woody mass about 11 cm. in diameter involved the greater portion of the lesser curvature and a part of the anterior surface of the stomach. A perforation was observed through the anterior gastric wall, close to the lesser curvature, near the incisura angularis. Numerous hard, discrete preaortic lymph nodes were palpated, but no other metastasis could be determined. A biopsy specimen was removed from the border of the gastric mass. The gastric necrosis and induration prohibited closure of the perforation by purse string sutures, so a patch of greater omentum was sutured over the perforative site, the free peritoneal fluid aspirated and the abdomen closed in layers, with a rubber dam drain to the involved area. Postoperatively a continuous Wangensteen nasal suction apparatus was set up, and adequate fluids were administered parenterally. The patient's course became progressively worse, and he died on the fourth postoperative day. Despite strenuous efforts, permission for a postmortem examination was refused. Microscopic section of the biopsy specimen taken at operation confirmed the gross diagnosis of carcinoma (fig. 1).

Case 2.—A. P., a 51 year old white man, was admitted to the City Hospital on Sept. 3, 1939, complaining of severe pain in the upper part of the abdomen, nausea and vomiting. The onset occurred about ten hours prior to entry and shortly after the evening meal. The pain was sudden and knifelike and was described as a "hit in the stomach" which "doubled up" the patient. There were no pains in the shoulders, and no fresh blood or "coffee ground" material was noted in the vomitus. He had never experienced pain of this type before but had been bothered by belching and indigestion for five months. Because of these ailments he attended a clinic in this city and was given frequent feedings of bland foods and some "powders." No roentgenograms were taken during this five month period. The patient stated that he had lost no weight, but this was not borne out by physical examination.

Examination revealed him to be slender and emaciated. He was obviously in acute distress, lying very still in bed and moaning rather loudly. Both hands were held over the upper part of the abdomen, and the examiner's attempts at palpation were warded off vigorously. The blood pressure was 100 systolic and 70 diastolic; the temperature was 98.8 F.; the pulse rate was 80, and the respiratory rate was 24. The thorax was essentially normal, and no hyperesthesia of the scapular regions was noted. The abdomen was boardlike in its rigidity and was splinted during respiration. The point of maximum tenderness lay over the epigastrium, though there was a rather diffuse abdominal rebound tenderness.

Auscultation revealed no peristalsis, and owing to the abdominal rigidity no intra-abdominal viscera could be palpated. Rectal examination revealed tenderness high in the anterior region above the prostate. The laboratory data were as follows: The urine showed no sugar, albumin or acetone; the white cell count was 19,900 and the red cell count 4,250,000 per cubic millimeter of blood; the Kahn test gave a negative reaction; the value for blood sugar was 89 mg. and that for

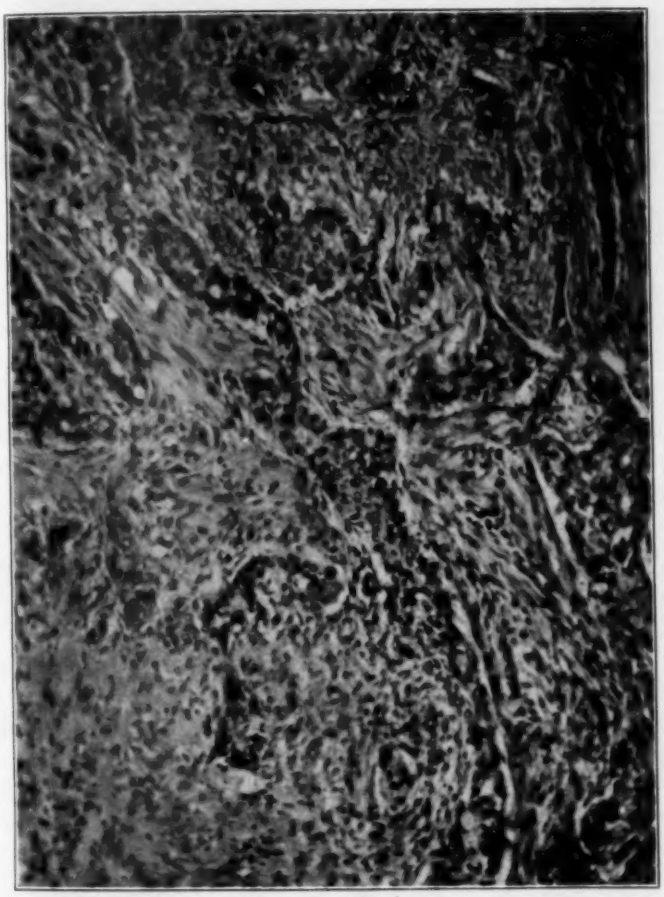

Fig. 2.—Microscopic section of a lymph node removed from the border of the greater gastric curvature, revealing sheets of invading epithelial cells. Though there is not a definite tendency to differentiation, certain of the epithelial islands appear to be arranged in acinar form.

nonprotein nitrogen 25 mg. per hundred cubic centimeters. A plate of the abdomen with the patient sitting failed to reveal the presence of free air under either leaflet of the diaphragm.

A diagnosis of perforated peptic ulcer was made, and after parenteral hydration the patient was subjected to an exploratory laparotomy. The abdomen was explored through an upper right rectus muscle-retracting incision. There was a

considerable amount of free cloudy fluid throughout the peritoneal cavity, and a layer of fibrinoplastic exudate covering the anterior surfaces of the stomach and transverse colon was noted. Along the lesser curvature of the stomach in its inferior and anterior extent was a hard, irregular mass approximately 10 cm. in diameter. In the center of this mass was a round perforation about 1 cm. in diameter. Numerous discrete, hard lymph nodes were present in both the lesser and the greater omentum, close to the gastric borders. Several large, hard nodes were also palpated along the preaortic area. There was no gross evidence of metastasis to the liver. The free peritoneal fluid was aspirated and an omental flap sutured over the perforative site. Two lymph nodes were removed from the greater omentum for microscopic section. The abdomen was closed in layers, with a rubber dam drain to the involved gastric surface.

The postoperative course was essentially uneventful, and the patient was discharged on the fourteenth day. On October 13 he reentered the hospital because of advanced emaciation and anorexia and died four days later, six weeks after the operation. Permission for a postmortem examination was refused. The biopsy specimen was reported as metastatic carcinoma of a lymph node (fig. 2).

COMMENT

In comparing the average age of all patients with gastric carcinoma with that of patients with carcinoma complicated by perforation there is a definite difference, the former falling in the sixth decade and the latter low in the fifth. The incidence of perforation in this series compares favorably with that in the much larger group reported by McNealy and Hedin.[2] It must be remembered that these authors, in giving a 4 per cent incidence, included both the classic and the obscure type, which were found to be approximately equal in incidence.

The 2 reported cases are interesting because of the close similarity in the histories, physical findings and operative descriptions. The lesions fall into the classic type with typical symptoms of generalized chemical peritonitis. The advanced stage of gastric involvement observed at operation would speak for a greater duration of the malignant process than is suggested by the relatively short (five month) period of symptoms. In a series of 168 cases of gastric carcinoma, Lahey [6] described a group of 53 lesions which were known to be in a fairly early stage, and of this number 32, or 60 per cent, had been producing symptoms for six months or less, while 21, or 35 per cent, had produced symptoms for six months or over. Lahey continued to state, however, that extensive malignant lesions of the stomach can occur with relatively few symptoms.

The differentiation of this condition from perforated peptic ulcer presents a real problem when the patients are first seen after perforation

6. Lahey, F. H.: Cancer of the Stomach, S. Clin. North America **14**:1033, 1934.

has occurred. Known gastric malignant tumors, observed in the hospital or elsewhere, with which sudden acute abdominal emergencies develop lend themselves to more accurate diagnosis. The differential diagnosis depends not so much on the physical findings as on the past history. McNealy and Hedin concluded that a history of rapid loss of weight and indigestion occurring in a middle-aged man who has suffered little, if any, from previous dyspepsia, weakness and epigastric pain is given considerable weight in diagnosing malignant perforation.

Immediate exploratory laparotomy is the therapy of choice. Should shock complicate the picture, parenteral fluids, blood transfusions and other combative methods must be used in an effort to prepare the patient for an early operation. Once the gastric lesion has been recognized and explored, further surgical steps must depend on the extent of the process and the condition of the patient. Ideally, gastric malignant tumors should be resected, but in the great majority of cases the consensus is represented by the opinion of Dickinson,[7] who stated that the primary operation should be limited to closure of the perforation, resection being reserved for a later time, when the patient is better able to withstand it. It is interesting to note that of the lymph nodes, grossly identical as to palpation and color, removed from the greater curvature of the stomach in the second case only one showed malignant invasion on microscopic section. The other node revealed chronic inflammatory changes. This certainly emphasizes the importance of the site of removal of the biopsy specimen.

Technically, closure of a perforation due to a gastric cancer is more difficult than closure of one due to a peptic ulcer. The former is more friable and indurated and does not lend itself to repair with a purse string suture or to other methods used in closure of a simple peptic ulcer. The simplest procedure is to cover the perforative site with a flap of greater omentum "tacked down" with interrupted absorbable sutures. After aspiration of the spilled gastric contents from the peritoneal cavity a rubber dam drain should be introduced to the region of the perforation with exit through a stab wound in the upper part of the abdomen. Drainage of the peritoneal cavity for ruptured peptic ulcers is a question depending on the lapse of time since perforation, the amount of peritoneal soiling and the surgeon; however, in the case of gastric malignant tumors which perforate, drainage is the procedure of choice in view of the fact that the latter cannot be closed with as much assurance that there will be no further leakage.

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7. Dickinson, A. M.: Perforation of Carcinoma of the Stomach, Surgery 5:544, 1939.

SUMMARY AND CONCLUSIONS

In a series of 247 proved gastric carcinomas there were 7 complicated by acute perforation and generalized peritonitis.

The average age of the patients in the entire group was 63 years, as compared with an average age of 51 years for the patients with perforation.

Two personal cases of perforated gastric carcinoma are presented in detail.

The differential diagnosis between gastric perforations due to carcinomas and those due to peptic ulcers is difficult if the patient is seen after perforation has occurred.

The initial operation should be limited to simple closure of the gastric perforation.

Biopsy specimens should be taken from all perforating gastric ulcers.

ISCHEMIC CONTRACTURE OF THE LOWER EXTREMITY

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The purpose of this communication is to report 2 cases of disabling deformities of the right lower extremity of eleven and fourteen years' duration respectively, presenting the following features: (1) healed fractures of the femur; (2) massive induration of the muscles of the leg and foot associated with atrophy and loss of motor power below the knee; (3) vascular dysfunction in the involved lower extremity; (4) contractural deformities of the foot and toes; (5) roentgen evidence of extraosseous calcification of the leg, and (6) histologic evidence (in 1 case) of massive degeneration of muscle tissue with fibrous tissue replacement and extensive calcification. In these cases there was a pathologic state in the lower extremity identical with Volkmann's ischemic contracture of the upper extremity.

REPORT OF CASES

CASE 1.—A white man 39 years old had sustained a fracture of the midshaft of the right femur eleven years previously. The fracture had been reduced by skeletal traction through the lower end of the femur, and this had been followed by immobilization on a Thomas splint for six months. Immediately after his injury he had noted swelling and ecchymosis of the right leg, pain in the right heel and numbness and coldness of the right foot, without disturbance in the color of the extremity. Shortly afterward he had noted loss of motor power in the foot and toes, marked firmness of the muscles of the leg and deformity of the right foot. The deformity recurred after a lengthening of the achilles tendon two years later. Despite prolonged physical therapy and the application of corrective shoes, his disability on weight bearing persisted.

Examination.—The right lower extremity presented a mild genu varum deformity with ½ inch (1.2 cm.) shortening, talipes equinocavovarus associated with multiple hammer toes, atrophy of the leg and foot and marked induration of all the muscles below the knee, especially in the extensor and peroneal compartments (fig. 1). A scar over the right heel represented the site of a healed pressure sore. Motion was normal in the knee but was almost entirely absent in the ankle and in the small joints of the right foot. Sensation was unimpaired, and there were no trophic changes. Reactions of degeneration were obtained in all the muscles below the knee. On the right side the femoral pulsation was easily palpable, but the popliteal, posterior tibial and dorsalis pedis pulses could not be obtained; all arterial pulses in the left lower extremity were normal. Oscillometric readings were diminished in the right lower extremity, but the cutaneous temperatures of the two feet were equal and normal.

Laboratory Data.—Blood Count: The value for hemoglobin was 85 per cent (Dare). There were 4,900,000 red blood cells and 8,900 white blood cells per cubic millimeter. The differential count was normal.

Urinalyses: The voided specimens were consistently normal, the specific gravity varying between 1.009 and 1.018.

Blood Chemistry: The value for calcium was 9.2 mg. and that for phosphorus 3.8 mg. per hundred cubic centimeters. The value for serum phosphatase was 4.9 Bodansky units. The value for nonprotein nitrogen was 29 mg., that for uric acid 3.3 mg. and that for cholesterol 167 mg. per hundred cubic centimeters.

The Wassermann and Kahn reactions of the blood were negative.

Roentgen Data.—Right Femur: There was a healed fracture of the midshaft, with slight malunion (fig. 2 *B*).

Right Fibula and Tibia: The bony structures and their associated joints were normal. There was extensive calcification of the soft structures on the anterolateral aspect, limited to approximately the middle three fifths of the leg and tending to be arranged in linear streaks lying in the longitudinal axis of the leg (fig. 2 *a*).

Right Foot: The bones and their joints were normal. There were equinus and cavus deformities and multiple hammer toe contractures (fig. 2 *C*).

Operation and Course.—Subcutaneous tenotomies of the achilles tendon and of the flexor and extensor tendons of the toes, subcutaneous plantar fasciotomy and dorsal exostectomy (internal cuneiform bone) of the right foot were performed without the use of a tourniquet. A biopsy was performed on the anterolateral aspect of the leg, about 6 inches (15 cm.) below the knee. The muscle tissue (tibialis anticus and extensor digitorum longus) was found to be replaced by yellowish white scar tissue which sectioned with difficulty, owing to the presence of considerable quantities of calcareous material. Plaster immobilization from the toes to the knee with the foot in corrected position was followed by physical therapy, massage and manipulation. All wounds healed by primary intention. The patient was greatly benefited by this operation but is prepared for a more extensive procedure in the event of a recurrence.

Histologic Picture.—Microscopic sections of the biopsy specimen from the leg were stained with hematoxylin and eosin, Van Gieson's stain and Weigert's elastic tissue stain. In a few areas scattered bundles of muscle fibers were still recognizable. These had undergone granular and hyaline degeneration, with partial or complete disappearance of their nuclei and loss of longitudinal and transverse striations. In the main, the muscle tissue was replaced by dense fibrous tissue containing scattered nuclei. In some areas this fibrous tissue had become revascularized. Interspersed among the bundles of collagenous fibers were small islands of finely granular calcific material (fig. 3). In other regions, which were poorly vascularized, cellular detail was no longer recognizable, and there was considerable necrotic debris, which took the eosin stain deeply. In such fields there were extensive areas of calcification (fig. 4). There were no inflammatory cells and no areas of hemorrhage. A few scattered large cells were filled with yellow pigment. There was no evidence of osteoid tissue or of immature or adult bone formation.

Case 2.—A white man 27 years old had sustained a transverse fracture of the right femur at the juncture of the middle and lower thirds of the shaft, with overriding and displacement of the fragments, fourteen years previously. An attempt at closed reduction followed by immobilization in plaster of paris had

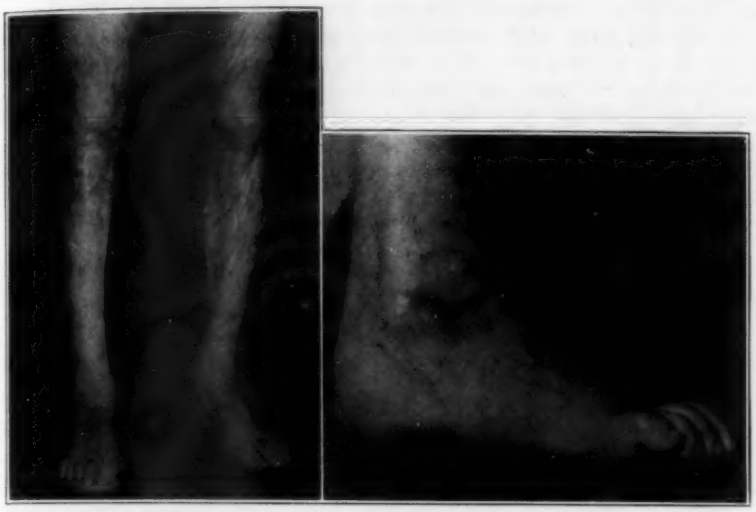

Fig. 1 (case 1).—Atrophy of the right leg with slight genu varum. There is an equinovarus deformity of the foot, with multiple hammer toes. The scar on the heel represents the site of a healed pressure sore.

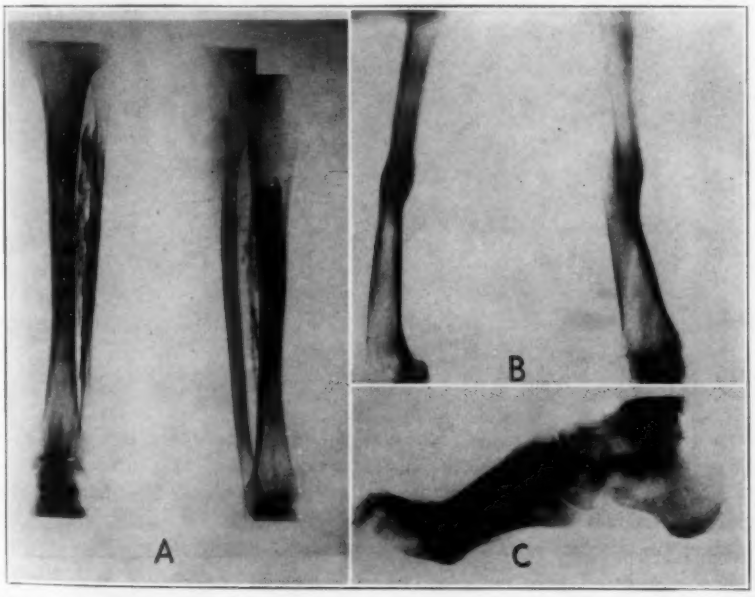

Fig. 2 (case 1).—Roentgenogram of (*A*) the right tibia and fibula, showing extensive calcification of the soft tissues on the anterolateral aspect, which tends to be arranged as linear streaks in the longitudinal axis of the leg; (*B*) the right femur, showing a healed fracture of the midshaft with some malunion, and (*C*) the right foot, illustrating the talipes equinocavus deformity with multiple hammer toe contractures.

been unsuccessful. Immediately thereafter the patient had experienced severe pain in his right leg distal to the fracture site, but he had noted no abnormal changes of color in the exposed toes. Two weeks later an open reduction had been performed under a tourniquet, and through a lateral incision the fragments had been fixed in good position by means of a steel ribbon band. The extremity was immobilized in plaster of paris. During the early postoperative period the patient experienced exquisite pain about the site of fracture despite the external fixation,

Fig. 3 (case 1).—Histologic section of a biopsy specimen of muscle from the right leg (× 50). The muscle tissue is entirely replaced by dense fibrous tissue with scattered nuclei and occasional blood vessels. An island of finely granular calcific material has been deposited at *a*.

and he noted inability to move actively the toes of the right foot. When the external fixative device was removed at the end of three months, he noted that the leg was atrophied and the muscles of the leg remarkably firm, that he was unable to move the foot and toes and that the foot became cold and cyanotic when pendant. There gradually developed a fixed equinovarus deformity of the

foot with multiple hammer toe contractures, and these deformities recurred after subcutaneous tenotomies on two occasions. Because of this deformity he had experienced increasing pain and disability on weight bearing.

Examination.—The patient walked with a limp on the right side due to a severe talipes equinovarus deformity with multiple hammer toes (fig. 5). The two lower extremities were of equal length, and the right femur was solidly united. There were considerable atrophy of the right leg and a boardlike rigidity of all the

Fig. 4.—Another field from the same biopsy specimen (× 50). There is hyaline degeneration of muscle fibers (*a*), which are fragmented and which have lost their nuclei and striations. In the main, the muscle tissue has been replaced by dense fibrous tissue (*b*) containing few nuclear elements and some new vascular channels. In some areas there is evidence of extensive necrosis (*c*) with widespread calcification (*d*).

muscles below the knee. The overlying skin was normal and freely movable. Motion in the knee joint was normal, but there was no active or passive motion in the ankle joint or in the joints of the foot and toes. The right leg and foot became slightly cyanotic when the extremity was pendant, and the right foot per-

Fig. 5 (case 2).—Atrophy of the right leg with an equinovarus deformity of the right foot and multiple hammer toe contractures. The dressings overlie two small ulcers produced by abnormal pressure on weight bearing.

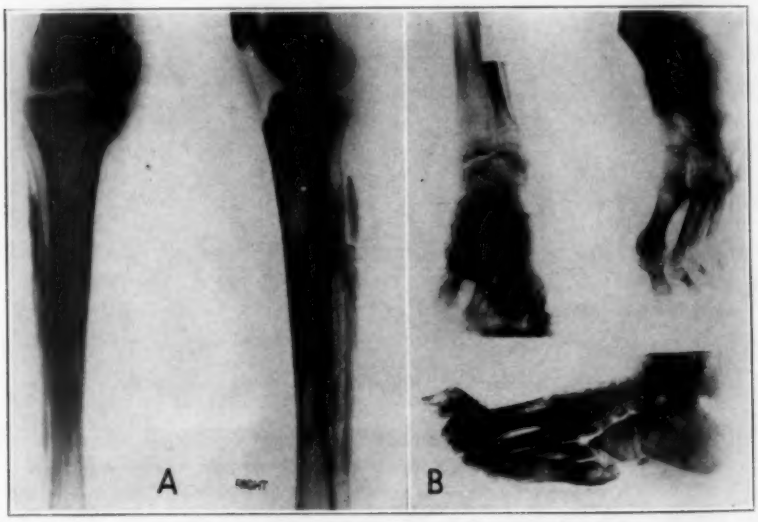

Fig. 6 (case 2).—Roentgenograms of (*A*) the right tibia and fibula, showing extensive calcification of the soft tissues, which tends to be arranged in linear streaks in the longitudinal axis of the leg, and (*B*) the right foot and ankle. The axis of the ankle joint is directed outward. The foot presents an equinus deformity, with varus of the anterior and posterior portions of the foot and multiple hammer toe contractures. The fourth and fifth metatarsal bones are hypertrophied and deformed.

spired more freely than the left, but the cutaneous temperatures and oscillometric readings for both lower extremities were normal. The femoral, popliteal, posterior tibial and dorsalis pedis pulses were normal bilaterally. There were small superficial ulcers in the region of the heel and beneath the head of the fifth metatarsal bone, the sites of preternatural weight bearing.

Laboratory Data.—The pertinent values for the blood and for the urine were normal.

Roentgen Data.—Lower End of Right Femur, Right Tibia and Right Fibula: There was extensive calcification of the soft tissues in the anterior, lateral and posterior portions of the right leg, occupying approximately the middle three fifths of the leg and arranged as linear streaks lying in the longitudinal axis of the leg. Where bony structures were not obscured by soft tissue shadows, they were roentgenographically normal (fig. 6 *a*).

Right Foot: The fourth and fifth metatarsal bones were hypertrophied and deformed. (These bones had been the site of major weight bearing.) The remaining bones and their joints were normal. There were talipes equinovarus and multiple hammer toe contractures (fig. 6 *b*).

Operation and Course.—Wedge resections were performed between the os calcis, astragalus, cuboid and navicular bones (triple fusion), and the hammer toes were corrected by multiple "flexor and extensor tenotomies," without the use of a tourniquet. A biopsy of the leg was not performed. Plaster of paris fixation from the toes to the knee was applied for three months until bony fusion was secured. A good anatomic and functional result was obtained.

LITERATURE

Previous reports and references have been tabulated in the accompanying table. It is not unlikely that the deformity in Cravener's [1] case was due to marked scarring incidental to repeated operative intervention and infection. The remarkable relief of pain and the disappearance of deformities of eighteen years' duration in Dieulafé's [2] case following periarterial sympathectomy suggest that this case may have been one of causalgia. The cases reported by Denucé [3] and by Riche, Aussiloux and Ginistié [4] presented atypical pictures of localized ischemic contractures involving the hamstring muscles, with resultant flexion deformities of the knee. In the second case reported by Jones and Cotton [5] no deformity developed, fasciotomy having been performed in the acute

1. Cravener, E. K.: Volkmann's Contracture of the Leg, New York State J. Med. **32**:381-382, 1932.

2. Dieulafé, R.: Syndrome de Volkmann du membre inférieur consécutif à la ligature de l'artère fémorale. Guérison par sympathectomie péri-iliaque, Bull. et mém. Soc. nat. de chir. **60**:473-474, 1934.

3. Denucé, M.: Contracture ischémique, Rev. d'orthop. **20**:97-146, 1909.

4. Riche, V.; Aussiloux, J., and Ginistié, J.: Syndrome de Volkmann du membre inférieur, Presse méd. **47**:1173-1175, 1939.

5. Jones, S. G., and Cotton, F. J.: Ischemic Paralysis of the Leg Simulating Volkmann's Contracture, J. Bone & Joint Surg. **17**:659-660, 1935.

Summary of Twenty Cases of Ischemic Contracture of the Lower Extremity

Author	Year of Report	Patient's Sex	Patient's Age, Years	Lower Extremity	Possible Initiating Factors	Duration of Deformity	Physical Findings	Vascular Lesion	Nerve Lesion	Operation and Results
Volkmann, R.: Krankheiten der Bewegungsorgane, in Pitha, F. J.; and Billroth, T.: Handbuch der allgemeinen und speciellen Chirurgie, Stuttgart, Ferdinand Enke, 1872, vol. 2, pt. 2, pp. 234-920, cited by Franceschelli	1872	Male	16	?	Hydrarthrosis of knee with flexion deformity; compression bandage	?	Talipes equinovarus (onset in less than one week)	None	None	None
Denucé [8]	1909	Male	15½	Left	Prolonged local exposure to low temperature (sitting on ice)	?	Flexion deformity of both knees, especially left; induration left hamstring muscles	None	None	Tenotomies of left hamstrings; good correction
Grieg [12] (case 1).....	1916	Male	9	Right	Contusion to leg with marked swelling and ecchymosis	1 year	Talipes equinovarus and multiple hammer toes; induration of calf; no active or passive motion in ankle and foot (deformity appeared 2 months after injury)	Dorsalis pedis and posterior tibial pulses not palpable	None	Tenotomies of achilles tendon and flexor tendons; slight relief
Grieg [13] (case 2).....	1916	Male	62	Left	Ligation of femoral artery in Hunter's Canal for popliteal aneurysm	?	Talipes equinovarus; atrophy and induration of calf; no active or passive motion in ankle joint (onset 7 months after ligation)	Foot and leg cold and cyanotic; dorsalis pedis and posterior tibial pulses not palpable	Hypesthesia of leg and foot	Tenotomy of achilles tendon and plantar fasciotomy; no relief
Souques [18]	1919	Male	21	Right	War wound on posterior surface of thigh in region of sciatic nerve; constricting bandage	1 year	Atrophy and "wooden" induration of calf; paralysis of extensor and peroneal muscles	Foot cold; diminished oscillometric readings	Common peroneal nerve paralysis	None
de Raffele: Le paralisi ischemiche, in Monografie dell'Instituto Rizzoli, Bologna, S. Capelli, 1923; cited by Franceschelli	1923	Male	23	Right	Fracture of right tibia at juncture of upper and middle thirds; constricting circular plaster bandage	?	Talipes equinovarus with multiple hammer toes; skin dry and adherent to underlying tissue; limited active and passive motion of foot (onset 50 days after trauma)	None	None	Exploration
Meyerding [6] (case 1)	1930	.....	..	.....	Fracture of tibia and fibula	..	No data	.....	.....	.....
Meyerding (case 2)	1930	.....	..	.....	Fracture of tibia and fibula	..	No data	.....	.....	.....
Meyerding (case 3)	1930				Fracture of tibia and	..	No data			

Meyerding [9] (case 1)	1930	.....	..	.....	Fracture of tibia and fibula	..	No data	.....	.....	.....
Meyerding (case 2)	1930	.....	..	.....	Fracture of tibia and fibula	..	No data	.....	.....	.....
Meyerding (case 3)	1930	.....	..	.....	Fracture of tibia and fibula	..	No data	.....	.....	.....
Cravener [1]	1932	Male	44	Right	Initial osteotomy of tibia and fibula for bowleg at 3; several reoperations	?	Atrophy of leg; talipes equinovarus; limited motion of ankle and toes	None	None	None
Dieulafé [2]	1934	Male	56	Right	Ligation of femoral artery in Scarpa's triangle for war wound	18 years	Talipes equinus and hammer toes; flexion deformity of knee; atrophy of calf; exquisite pain in calf and heel	Diminished oscillometric readings	Areas of hypesthesia and anesthesia of leg	Right external iliac periarterial sympathectomy; recovery
Jones and Cotton [5] (case 1)	1935	Male	45	Right	Severe crush injury of popliteal region	About 1 year	Talipes equinus; atrophy and induration of muscles below the knee	No pulses distal to groin; color changes in foot and diminished cutaneous temperature	Disturbed sensation; recovery in 1 year	Tenotomy of achilles tendon
Jones and Cotton [5] (case 2)	1935	Male	45	Left	Severe crush of popliteal region; fracture of left fibula	..	No deformity	No pulsations distal to the groin; coldness and ischemia	Hypesthesia	Immediate fasciotomy (popliteal); complete recovery
Guyot, J.; Villar, J.; Chavannaz, J., and Courriades, H.: Sur un cas de syndrome de Volkmann du membre inférieur gauche, J. de méd. de Bordeaux **112**: 689, 1935	1935	Male	47	Left	Fracture internal tuberosity of tibia	Less than 1 month	Talipes equinus; flexion deformity of knee; induration of calf muscles; pain in leg and foot	None	Hypesthesia of dorsum of foot	None
Franceschelli, N.: La retrazione ischemica di Volkmann dell'arto inferiore, Ortop. e traumatol. dell'app. mot. **7**: 461-481, 1935	1935	Male	28	Right	Fracture tibia and fibula with delayed union and final malunion; constricting plaster bandage	About 7 months	Talipes equinovarus with multiple hammer toes; induration of calf muscles	Slight alteration in pressure and oscillometric readings	Hypesthesia of foot	None
Griffiths [14]	1938	Male	67	Left	Embolism of femoral artery, secondary to auricular fibrillation and thyrotoxicosis	1 month	Equinus deformity with multiple hammer toes; induration of calf muscles (deformity appeared shortly after recovery of circulation)	Complete interruption of circulation; almost complete recovery 4 days after embolectomy (performed 17½ hrs. after onset); all peripheral pulses palpable, except posterior tibial	None	Manipulation of foot and plaster fixation; complete recovery

Summary of Twenty Cases of Ischemic Contracture of the Lower Extremity—Continued

Author	Year of Report	Patient's Sex	Patient's Age, Years	Lower Extremity	Possible Initiating Factors	Duration of Deformity	Physical Findings	Vascular Lesion	Nerve Lesion	Operation and Results
Franceschelli [19]	1939	Male	53	Right	Fracture of tibia and fibula at juncture of middle and lower thirds; first plaster cast removed shortly after application because of pain and multiple wounds of the leg; fractures united in 4 months, second cast having been applied after healing of all wounds	3 years	Equinocavovarus deformity of foot and flexion deformities of all toes; induration of muscles of leg (deformity noted after removal of first plaster cast)	None	None	Amputation of toes; lengthening of achilles tendon and plantar fasciotomy; excellent functional and cosmetic result
Riche and others [4]	1939	Male	42	Right	Multiple injuries, including fracture of the pelvis and compound fracture of both bones of leg	5 months	Painful flexion deformity of knee; induration of hamstring muscles; nonunited leg fracture; trophic ulcers of leg	None	None	Amputation
Horwitz (this paper)	1940	Male	39	Right	Fracture of femur in midshaft; contusion of leg with marked swelling and ecchymosis	11 years	Talipes equinocavus with multiple hammer toes; atrophy of leg and induration of leg muscles; little motion in ankle and foot joints	No pulsations distal to groin; diminished oscillometric readings	None	Multiple tenotomies of achilles tendon and toes and plantar fasciotomy; dorsal exostectomy; good result
Horwitz (this paper)	1940	Male	27	Right	Fracture femur 6 inches (15 cm.) above knee; unsuccessful closed reduction; open reduction under tourniquet	14 years	Talipes equinovarus with multiple hammer toes; induration and atrophy of entire leg and foot; superficial ulcers of heel and beneath 5th metatarsal head	Cyanosis of skin; normal peripheral pulses and oscillometric readings	None	Triple fusion and multiple tenotomies of toes; good result

(prodromal) stage. Meyerding [6] referred to 3 cases in which the condition followed fractures of the tibia and fibula but offered no details. The clinical features of the deformities of the lower extremity observed in my 2 cases were present, in whole or in part, in the remaining 10 cases.

COMMENT

Etiology.—It is generally accepted that the mechanogenesis of ischemic contracture is dependent in whole or in part on acute venous obstruction. This concept has been substantiated by the experimental evidence of Brooks [7] and of Middleton,[8] who produced a condition resembling ischemic contracture of muscle by sudden venous obstruction. Jepson [9] and Burman and Sutro [10] noted that venous stasis alone is not sufficient to produce such contractures permanently but that, in addition, proximal constriction of the soft tissues is necessary. Brooks, Johnson and Kirtley [11] and Wilson [12] noted the development of contractures in experimental animals after arterial ligation, which appeared later than those produced by acute venous obstruction and were attended by a less severe degree of inflammation. Clinical reports substantiate the concept that arterial obstruction may produce ischemic contractures in certain instances (Grieg,[13] case 2; Dieulafé;[2] Griffiths [14]). That arterial and venous interruption may occur concomitantly in the acute stage was demonstrated at operation by Jones and Cotton [5] in their second case.

The fundamental factors, therefore, are abnormal pressure conditions in a space containing muscles surrounded by resistant fascia and by

6. Meyerding, H. W.: Volkmann's Ischemic Contracture, J. A. M. A. **94**:394-400 (Feb. 8) 1930.

7. Brooks, B.: Pathologic Changes in Muscle as a Result of Disturbances of Circulation: An Experimental Study of Volkmann's Ischemic Paralysis, Arch. Surg. **5**:188-216 (July) 1922.

8. Middleton, D. S.: The Pathology of Congenital Torticollis, Brit. J. Surg. **18**:188-204, 1930.

9. Jepson, P. N.: Ischemic Contracture: Experimental Study, Ann. Surg. **84**:785-795, 1926.

10. Burman, M. S., and Sutro, C. J.: Experimental Ischemic Contracture, Ann. Surg. **100**:559, 1934.

11. Brooks, B.; Johnson, G. S., and Kirtley, J. A.: Simultaneous Vein Ligation: An Experimental Study of the Effect of Ligation of the Concomitant Vein on the Incidence of Gangrene Following Arterial Obstruction, Surg. Gynec. & Obst. **59**: 496-499, 1934.

12. Wilson, W. C.: Occlusion of the Main Artery and Main Vein of a Limb, Brit. J. Surg. **20**:393-411, 1932.

13. Grieg, D. M.: Two Cases of Ischemic Contracture of Unusual Origin, Clin. J. **45**:361-363, 1916.

14. Griffiths, D.: Arterial Embolism: A Study of Eight Cases, Lancet **2**:1339-1344, 1938.

bone and drained of blood by a peculiar anatomic arrangement which favors obstruction. The thin-walled veins collapse more readily than the heavier-walled arteries. Middleton [8] has discussed this mechanism in the upper extremity at the bend of the elbow, where a venous plexus with a diameter of about 2 cm., when compressed, will lead to obstruction of the venous drainage from the deep structures of almost the entire forearm. The comparative inextensibility of the aponeurotic compartments of the forearm may likewise embarrass venous return in the presence of hemorrhage and edema incidental to fractures of the forearm (Garber [15]).

The same susceptibility for venous interruption is noted in the closed fascial compartments of the popliteal space and of the leg. After dissection of the lower extremities of several human cadavers, I suggest the following sites for such susceptibility:

1. Where the popliteal vein lies posterolateral to the popliteal artery within the popliteal space, in juxtaposition to the posterior surface of the external femoral condyle. Compression at this level would interfere with the venous return from all the muscles of the leg and foot.

2. Where the popliteal vein lies ventral to the soleus muscle at the latter's origin from the prominent popliteal line. This would interrupt the venous return from all the muscles of the leg and foot except the medial and lateral heads of the gastrocnemius muscle.

3. Where the anterior tibial vein or veins perforate the interosseous membrane and pass between the two heads of the tibialis posticus or between this muscle and the fibula to join the posterior tibial vein or veins. This would interfere with venous drainage from the anterior and lateral muscle groups of the leg.

In a review of the literature, Hill and Brooks [16] collected 123 cases in which ischemic contracture had developed without previous application of a constricting bandage and 26 cases in which there had been no fracture. In the cases of involvement of the lower extremity collected in this article, a constricting bandage was the most likely factor in 1 case and might have been an influential factor in 4 more. In 3 cases there had been severe injuries to the soft tissues of the popliteal region or the calf, in 2 without fractures and in 1 with a simple fracture of the upper end of the fibula. In 7 cases there had been fractures of one or both bones of the leg, in 1 case a fracture of the femur at the juncture of its middle and lower thirds and in 1 case a fracture of the femur at its midshaft and a severe contusion to the calf.

15. Garber, J. N.: Volkmann's Contracture as a Complication of Fractures of the Forearm and Elbow, J. Bone & Joint Surg. **21**:154-168, 1939.

16. Hill, R. L., and Brooks, B.: Volkmann's Ischemic Contracture in Hemophilia, Ann. Surg. **103**:444-449, 1936.

Peripheral nerve lesions are not considered important factors in the causation of this condition. They may complicate the clinical picture if the nerve has been injured at the time of initial trauma or if the nerve has become involved secondarily in scar tissue. Sensory lesions are not as a rule anatomically defined and are believed to be due to circulatory disturbances rather than to peripheral nerve lesions.

Leriche [17] and his followers consider injury to the sympathetic fibers in the arterial walls to be a greater factor than actual mechanical interference with the blood supply of the muscles. The good results reported by them as following periarterial sympathectomy and arteriectomy are difficult to explain in view of present anatomic knowledge and have been attributed by the antagonists of this theory to the coincidental fasciotomy. It would appear that surgical intervention on the sympathetic nervous system should be confined to those cases in which the condition is complicated by vasomotor instability or by causalgia.

The wisdom of fasciotomy during the acute (prodromal) stage, in the lower extremity as in the upper extremity, appears to be substantiated by the recovery and the avoidance of contractural deformities in the case reported by Jones and Cotton [5] after exposure of the popliteal space and evacuation of its extravascular bloody contents. If the dreaded contracture is to be avoided, pressure must be relieved immediately, as soon as the earliest evidence of impending vascular interference becomes recognizable.

Clinical Picture.—The features of the acute stage in the lower extremity, as in the upper extremity, are pain, cyanosis, edema, paresthesias, hypesthesias, loss of motor power and trophic disturbances. In the residual stage the muscles become rigid and contracted. In the forearm this affects mainly the long flexor muscles of the fingers and thumb and the pronator muscles, and there result flexion deformities of the elbow, wrist and interphalangeal joints, with extension deformities of the metacarpophalangeal articulations and pronation contracture of the forearm. In the lower extremity, with involvement of the muscles below the knee an identical deformity is produced, with equinus at the ankle, cavus and varus of the foot and multiple hammer toe contractures. In the atypical cases in which ischemic contracture is limited to the hamstring muscles there are flexion contractures of the knee joint. In the stage of contracture, hypesthesia, trophic changes and evidences of vascular dysfunction (organic or vasomotor) may persist. Peripheral pulsations were not obtainable distal to the groin in 3 previously reported cases and in my first case. Intractable pain was a serious feature in 2

17. Leriche, R.: Rétraction isolée des fléchisseurs et des pronateurs après fracture sus-condylienne de l'humérus et rupture sèche de l'artère humérale. Artériectomie. Guérison, Bull. et mém. Soc. nat. de chir. **54**:212-216, 1928.

reported cases, leading to amputation in 1 (Riche and his associates [4]); in the other it was relieved by periarterial sympathectomy (Dieulafé [2]). A definite nerve lesion (common peroneal nerve) complicated the ischemic contracture in 1 case (Souques [18]).

Histologic Features.—The pathologic changes in the muscle during the acute stage are edema, infiltration of the interfibrillary spaces with leukocytes, disappearance of the nuclei of the sarcolemma, loss of muscle striations and granular and hyaline degeneration with atrophy and fragmentation of the muscle fibers. The pathologic features of the muscle in the stage of contracture are well exemplified in a biopsy specimen removed by me from the forearm of an 18 year old Negro with an ischemic contracture of the forearm and hand following a crush injury of the elbow region two years previously. Sections showed fragmentation and atrophy of the muscle bundles, with cloudy swelling and hydropic degeneration. The muscle nuclei stained poorly or had disappeared. In large areas the muscle tissue was replaced by dense, moderately vascular fibrous tissue in which were scattered islands of round cells and occasional large cells containing yellow pigment. In some areas there was calcification of the vessels, with necrosis. (Calcification of the soft tissues was evident on the roentgenogram.)

Histologic sections of the muscle from the lower extremity amputated by Riche, Aussiloux and Ginistié [4] showed areas of atrophy and swelling of the muscle fibers, with loss of striations and absence of inflammatory cells. Franceschelli [19] (1939) studied biopsy specimens from the tibialis anticus, triceps surae and plantar muscles of the involved leg of his patient, and these showed varying degrees of degeneration of the muscle fibers with proliferation of the interstitial connective tissue. There were no demonstrable changes in the achilles tendon or in the plantar fascia. The features of the biopsy specimen removed in my case represented a very advanced stage; there were massive replacement of degenerated muscle fibers by relatively avascular and acellular fibrous tissue and areas of extensive necrosis and calcification.

Such extraosseous calcification in the forearm and leg, representing the dystrophic form of pathologic calcification, is characterized by the deposit of lime salts in tissue of low viability or in dead tissue. Available evidence indicates that this process is associated with vascular deficiency and is dependent on such local factors as hydrogen ion concentration and carbon dioxide tension and that it is not related to general changes in calcium-phosphorus metabolism, to the state or amount of calcium

18. Souques, A.: Un cas de maladie de Volkmann au membre inférieur, Rev. neurol. **35**:451-453, 1919.

19. Franceschelli, N.: Retrazione ischemica dell'arto inferiore, Arch. di ortop. **55**:348-357, 1939.

and phosphorus in the circulating blood or to dysfunction of the parathyroid glands or of the kidneys. (The laboratory data in my cases showed uniformly normal values.)

SUMMARY AND CONCLUSIONS

Two cases of ischemic contracture involving the lower extremity are reported. From these cases and a review of 18 previously reported cases the clinical, roentgen and pathologic features of this condition are defined. Its occurrence must be anticipated after fracture or extensive injury to the soft tissues without fracture in the lower extremity, especially in the region of the knee and leg. The stage of contracture and deformity may be avoided by fasciotomy during the acute (prodromal) stage. Deformities of the lower extremity consequent on the contractures may be corrected by adequate nonoperative and operative measures.

FACTOR OF BILE STASIS IN EXPERIMENTAL PRODUCTION OF GALLSTONES IN DOGS

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For the study of the origin of cholecystitis a method was devised which allowed introduction of material into the gallbladders of experimental animals (dogs) without causing appreciable damage to the wall of the gallbladder.[1] This method consisted of leading a fine rubber catheter through an incision in the common duct into the cystic duct and into the gallbladder and, after withdrawal of the catheter, restoring a fairly normal flow of bile by inserting a glass cannula into the common duct. The animals were killed after two to five days. Absence of infection and dilatation of the biliary system was noted in a large number of control animals.

In order to study the effect which long-standing cannulation might have on the biliary system, 3 of these dogs, together with 2 others, in which cholecystectomy was performed in addition to insertion of the cannula, were kept alive for a period ranging from sixteen months to two years. When the animals were killed at the end of the observation period, precipitates were found in the cannula and in 1 instance in the gallbladder. Though these precipitates could not be called stones in the proper sense of the word, there was sufficient resemblance to make description and discussion of these experiments worth while.

Numerous attempts have been made by many authors to produce gallstones in the experimental animal, but none has ever been entirely successful. Gilbert,[2] Gilbert and Fournier[3] and Mignot[4] infected the gallbladders of dogs, rabbits and guinea pigs with either Bacillus typhosus or Bacillus coli and produced concretions; Rosenow[5] obtained similar results, using streptococci in rabbits. No description of these experiments, however, is given in any of the reports. Richardson and Cushing[6] obtained stones by injecting Bacillus typhosus directly into

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This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research.

1. Aronson, H. G., and Andrews, E.: Proc. Soc. Exper. Biol. & Med. **32**: 1629, 1935.
2. Gilbert, A.: Arch. gén. de méd. **10**:257, 1898.
3. Gilbert, A., and Fournier, L.: Compt. rend. Soc. de biol. **4**:936, 1897.
4. Mignot, R.: Arch. gén. de méd. **10**:129, 1898.
5. Rosenow, E. C.: J. Infect. Dis. **19**:527, 1916.
6. Cushing, H.: Bull. Johns Hopkins Hosp. **1**:166, 1899.

the gallbladder of the rabbit in only 1 instance. Wilkie [7] produced a calcium precipitate in the gallbladder by ligation of the cystic duct and injection of anhemolytic streptococci into the gallbladder. Phemister, Day and Hastings [8] produced calcium carbonate concretions by ligation of the cystic duct and injection of anhemolytic streptococci into the gallbladder.

The colloidal chemical theory advocated by Aschhoff, Bacmeister, Shade and many others has found even less experimental support. Reports on concretions produced by feeding experiments are scarce and inconsistent.

Foreign bodies frequently become the nuclei of precipitation in bile. Kretz [9] reported "stone formation" on thread left at operation in the gallbladders of rabbits and dogs. This agrees with my own observation. Whenever nonabsorbable suture material was used for closure of incisions in the gallbladder or in the common duct, the free ends of the sutures, which were in contact with bile, became coated with dark incrustations. Rous and his co-workers [10] also obtained concretions in dogs which were due to the action of a foreign body. They found precipitations resembling stones in the glass cannula inserted in the common duct and frequently in a long rubber tube attached to the cannula and leading to a collecting bag outside the abdomen. Though these stones were never found "in the biliary system proper," the study is of great interest, since the authors excluded certain factors, such as activity of the gallbladder and infection. Considering the length of the tubing used, it seems doubtful, however, that stasis of bile was absent in their experiments. The concretions were carefully analyzed, and it was found that phosphorus and cholesterol were always absent, while carbonates were found in some and "much calcium" and pigment in most of them. The pigment was described as showing the features of bilirubin-calcium as described by Städeler,[11] being insoluble in ether or chloroform and becoming soluble in chloroform after treatment with weak acid. Because of this solubility behavior and the presence of much calcium in the residue, the authors concluded that originally bilirubin-calcium was present.

I. CANNULATION OF THE COMMON DUCT

Method.—Insertion of the cannula was performed as follows:

With ether anesthesia and strictly aseptic conditions, the abdomen of the dog was opened by a midline incision, and the common duct was incised longitudinally

7. Wilkie, A. L.: Brit. J. Surg. **15**:450, 1928.
8. Phemister, D. B.; Day, L., and Hastings, A. B.: Ann. Surg. **96**:595, 1932.
9. Kretz, R., in Krehl, L., and Marchand, F.: Handbuch der allgemeinen Pathologie, Leipzig, S. Hirzel, 1913, vol. 2, pt. 2, p. 493.
10. Rous, P., and McMaster, P. D.: J. Exper. Med. **37**:11, 1923.
11. Städeler, G.: Ann. d. Chem. **132**:323, 1864.

close to the duodenum. A soft French rubber catheter was introduced into the gallbladder; 10 to 15 cc. of bile was aspirated by means of a syringe, and an equal amount of physiologic solution of sodium chloride was injected into the gallbladder. The catheter was then withdrawn, and a glass cannula was inserted and tied circular into the opening which had been made in the common duct.

In some instances the gallbladder was removed after cannulation of the duct.

PROTOCOLS

Dog 1.—A cannula was implanted in the common duct. The observation covered fourteen months. The dog remained in good condition for about ten months, then became jaundiced and gained weight rapidly. It was electrocuted.

Postmortem Study.—There was more than 5 gallons (20 liters) of watery, slightly bile-stained fluid in the abdomen. The gallbladder and the ducts were dilated, and the wall was thickened; on opening there were scar formation and a high degree of stenosis of the common duct where it had been opened. The cannula was not found in the body; consequently it must have passed by the bowel. There was a high degree of cholangitic cirrhosis of the liver.

Dog 2.—The observation covered two years. The dog was in excellent condition throughout. There was no jaundice. The animal was electrocuted.

Postmortem Study.—The choledochus was not stenosed. The ducts and gallbladder were not dilated and were free of deposits. The cannula was not found.

Dog 3.—A cannula was implanted in the common duct. The observation covered sixteen months. The dog was in good shape, without jaundice. It was electrocuted.

Postmortem Study.—There was slight dilatation of the gallbladder and of the ducts. There was thickening of the walls of the ducts; on opening there was some narrowing in the common duct where the cannula had been inserted. The cannula was not found. The gallbladder contained greenish bile, with two hard, somewhat friable concretions. The larger was 8:3 mm. in diameter; the smaller, 2:2 mm. Analysis of the concretions revealed strongly positive reactions for cholesterol and calcium; a positive reaction for pigment; a trace of phosphorus, and a proportionately large amount of residue, unaccounted for.

Dog 4.—Cholecystectomy and insertion of a cannula in the common duct were performed. The observation covered nineteen months. The dog was in good condition and not jaundiced. It was killed.

Postmortem Study.—The ducts were slightly dilated. The cannula was found free in the common duct, with sutures around it which had cut through the duct. The cannula was covered with dark, hard incrustations on the inner and outer surfaces. The lumen of the cannula was somewhat narrowed but sufficiently patent to allow a fairly free flow of bile. Analysis of the incrustation revealed a trace of cholesterol; calcium, 1.1 per cent; a trace of pigment, and negative reactions for iron and phosphorus. There was a large amount of black residue, unaccounted for.

Dog 5.—Cholecystectomy and insertion of a cannula in the common duct were performed. The observation covered nineteen months. The dog was in good condition and not jaundiced. It was killed.

Postmortem Study.—The observations were practically the same as in dog 4. Analysis of incrustation revealed a trace of cholesterol; calcium, 0.5 per cent; a

trace of pigment, and negative reactions for iron and phosphorus. There was a large amount of black residue, unaccounted for.

COMMENT

One of 5 dogs in which a cannula was inserted into the common duct showed after sixteen months a cholangitic cirrhosis due to cicatricial stenosis of the common duct. The 4 other dogs remained in excellent

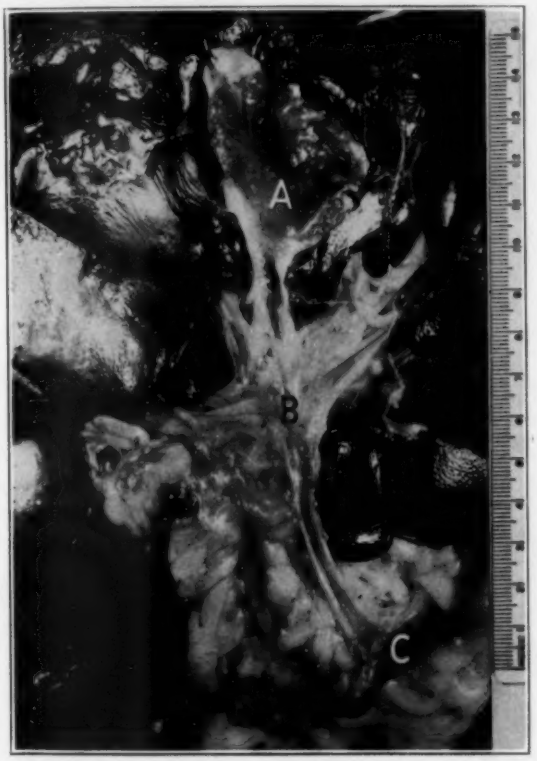

Fig. 1 (dog 2).—The common duct was cannulated two years. The cannula was lost. The gallbladder and ducts, when opened, showed no dilatation. *A*, gallbladder; *B*, site of insertion of the cannula; *C*, duodenum.

condition, without clinical signs of biliary obstruction. When they were killed, from sixteen months to two years after operation, the duct system was found to be patent. In only 1 instance were there a slightly stenosing scar in the common duct and dilatation of the gallbladder (dog 3). The same dog also revealed two small hard stones in a grossly noninflamed gallbladder. On chemical examination these concretions were shown to contain cholesterol, calcium, some pigment, a trace of phosphorus and

unaccounted for residue. As gallstones have never been found to occur naturally in a dog's gallbladder, it seems that these stones were artificially produced. A likely cause for their formation is stasis. It is furthermore of interest that the cannula was found in place only in those dogs in which the gallbladder had been removed. The gallbladder therefore, acting as a "vis a tergo," was responsible for forcing the cannula out of the common duct. Analysis of the incrustations formed in the cannula

Fig. 2 (dog 4).—Cholecystectomy and cannulation of the common duct for nineteen months were performed. The cannula, covered with incrustations, was lifted out of the duct. *A*, site where the gallbladder was removed; *B*, cannula; *C*, duodenum.

revealed in both cases small quantities of calcium and pigment and a comparatively large amount of a residue not accounted for. The only factors in the formation of these concretions appeared to be the slowing down of the flow of bile and the presence of the foreign body. The concretions were somewhat similar to stones found in the human bile duct system, in that both were low in cholesterol and calcium. A large

amount of residue is also found in most human gallstones. My recent studies seem to indicate that this residue constitutes polymerized bile pigment.[12] The slowing down of the flow of bile as well as the presence of the foreign surface appears to be responsible for the formation of these concretions, possibly by polymerizing the bile pigment. These concretions also resemble those produced by Rous in the cannula and rubber tube, though less pigment could be extracted in my experiments.

Fig. 3 (dog 5).—Cholecystectomy and cannulation of the common duct were performed. The period was nineteen months. The cannula, covered with incrustations, was found loose in the common duct. *A*, site where the gallbladder was removed; *B*, cannula; *C*, duodenum.

II. FACTOR OF STASIS IN PRECIPITATION OF BILE

In the previous study I was able to show that a cannula implanted and retained for a long period in the common duct of the dog became

12. Aronson, H. G.: A Component of Gallstones Insoluble in Ordinary Solvents and Accounting in Part for Their Dark Coloration, Arch. Path. **30**:726 (Sept.) 1940.

coated with concretions on its inner and outer surfaces. In these experiments the gallbladder had been removed, and it was obvious that the elimination of expulsive action from the ducts produced by contraction of the gallbladder had played a part in the formation of these concretions.

In 1 dog two small stones had formed in the gallbladder, which was somewhat dilated secondary to implantation of a cannula followed by expulsion and partial obstruction (cicatrization) of the common duct.

In order to analyze further the effect local stasis might have on precipitation of bile, the following experiments were carried out.

Method.—A glass cannula with a bulb arising from one side of its middle was inserted in the common duct, and the bulb was wrapped in omentum. The size of the bulb varied from ⅓ inch by 3 inches (0.8 by 7.6 cm.) to 2½ by 3 inches (6.2 by 7.6 cm.), and the neck between the bulb and the cannula was ⅓ inch (0.8 cm.) in diameter. This opening was large enough to allow free flow of bile from the duct into the bulb. It is obvious that bile in the bulb would be somewhat stagnant.

PROTOCOLS

Dog 6.—A cannula with a bulb (1½ by 2 inches [3.2 by 5 cm.]) was inserted. The observation covered sixty days. The dog was losing weight but was not jaundiced. It was killed.

Postmortem Study.—The bulb was filled with light green bile and dark sediment. The ducts and gallbladder were dilated. The ducts contained green bile; the gallbladder, dark brown bile. No obstruction was found in the ducts. Analysis of bile from the gallbladder revealed a value for pigment of 150 mg. and a value for calcium of 47 mg. per hundred cubic centimeters. Bile from the ducts contained 75 mg. of pigment and 33 mg. of calcium per hundred cubic centimeters. Bile from the bulb contained 135 mg. of pigment and 15 mg. of calcium per hundred cubic centimeters.

Dog 7.—A cannula with a bulb (2½ by 3 inches [3.2 by 5 cm.]) was inserted. The observations covered ten days. The dog died.

Postmortem Study.—There was peritonitis, with bile-stained fluid; there was no visible perforation. The bulb was filled with thin green bile. There was a small black precipitate on the inside of the neck, where the bulb connected with the cannula. Chemical analysis of the precipitate revealed a negative reaction for cholesterol; positive reactions for pigment and calcium, and a large amount of black residue.

Dog 8.—A cannula with a bulb (⅓ inch by 2 inches [0.8 by 5 cm.]) was inserted. The observation covered ten days. The dog had distemper. It was killed.

Postmortem Study.—The cannula was filled with dark bile of high viscosity and some evenly distributed coagulated matter. There was a dark, precipitated mass in the end of the bulb. Chemical examination of the precipitate showed some pigment; calcium, 1.5 per cent, and a large amount of black residue, unaccounted for. Analysis of bile from the gallbladder revealed a value for pigment of 125 mg. and a value for calcium of 54 mg. per hundred cubic centimeters. Bile from the bulb contained 78 mg. of pigment and 37 mg. of calcium per hundred cubic centimeters.

Dog 9.—A cannula with a bulb (⅓ inch by 2 inches [0.8 by 5 cm.]) was inserted. The observation covered five and one-half months. The dog was in good condition. It was killed.

Postmortem Study.—There was some dilatation of the gallbladder. The common duct and the bulb were imbedded in omentum. A thick fibrous capsule covered the glass. When the common duct was opened the cannula was surrounded by thickened bile. The ligatures around the common duct had cut through the duct and were found on the cannula. The gallbladder contained dark bile and numerous black, friable concretions, measuring 1 to 3 mm. (fig. 5). The cannula and the

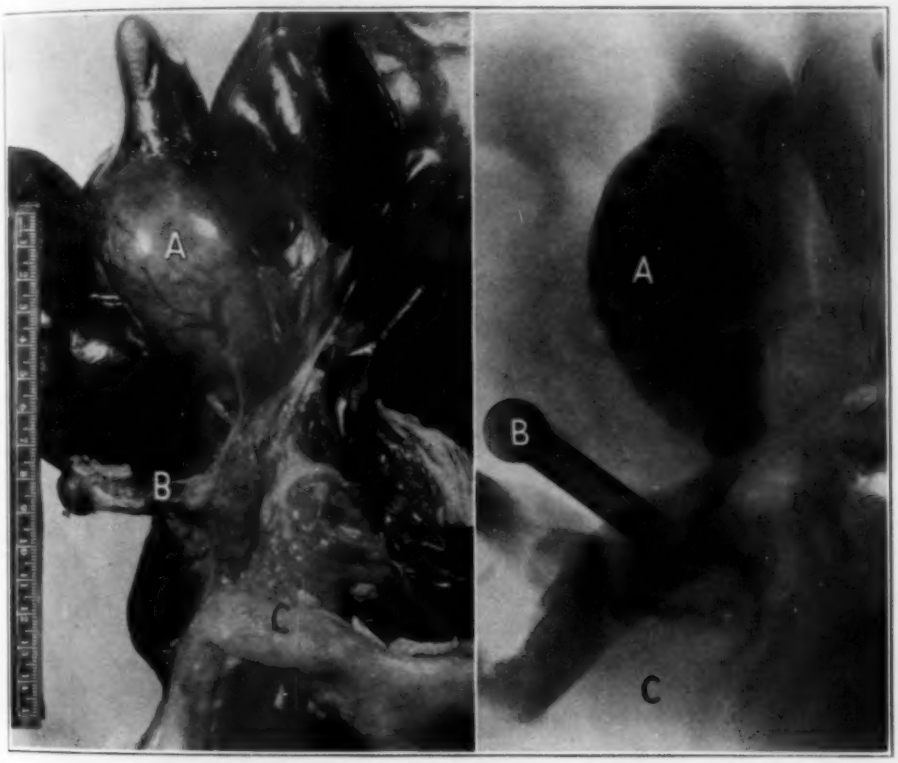

Fig. 4 (dog 9).—Photograph, cannula with a bulb in the common duct at five and one half months. There was slight dilatation of the gallbladder and ducts. *A*, gallbladder; *B*, bulb arising from the cannula in the common duct; *C*, duodenum. Roentgenogram, same specimen. *A*, gallbladder; *B*, cannula; *C*, duodenum.

bulb contained liquid bile (with increased viscosity) and some coagulated matter. Chemical analysis of the concretions in the gallbladder showed a trace of cholesterol; a trace of pigment; calcium, 5.9 per cent, and a large amount of black residue, unaccounted for. Analysis of the coagulated matter in the cannula and in the bulb showed: cholesterol, 5.3 per cent; pigment, 0.3 per cent; calcium, 0.3 per cent; a trace of phosphorus, and residue (by difference) 94 per cent.

Dog 10.—A cannula with a bulb (⅓ inch by 3 inches [0.8 by 5 cm.]) was inserted. The observation covered five months. The dog was in good condition. It was killed.

Postmortem Study.—The gallbladder and ducts were not dilated. A fibrous capsule had formed around the bulb. There was dark green bile with coagulated matter in the gallbladder.

COMMENT

Though the flow of bile in the glass bulbs was slowed, the changes in the bile were slight and inconsistent. The bile remained liquid in all bulbs, and in only 2 instances (dogs 8 and 9) was its viscosity markedly increased. Precipitation had occurred in only 2 instances, once in the form of a dark sediment (dog 6) and once as a precipitated mass

Fig. 5 (dog 9).—Concretions found in the gallbladder, resulting from partial obstruction of the common duct. The cannula had been inserted in the common duct for five and one-half months.

(dog 8) weighing 8 mg. total. This mass was low in calcium but contained a large amount of residue. In dog 7 a small concretion of similar composition was found on the edge where the cannula and the bulb connect. Both of these resembled the incrustations on the cannula described in the first part of this study.

Concretions in the gallbladder itself were found in 1 experiment, in which the cannula had caused partial obstruction of the duct with marked dilatation of the gallbladder. These concretions contained comparatively much calcium (5.9 per cent) and resembled the concretions formed in the gallbladder of the dog in which stenosis of the common duct had been produced by a cannula.

SUMMARY

In 3 dogs with a glass cannula inserted in the common duct after cholecystectomy the flow of bile remained fairly normal during an observation period of from sixteen months to two years.

The cannula had worked out of the duct in 2 other cases in which the gallbladder had not been removed.

One animal of group 2, showing slight stenosis due to scar formation in the common duct and dilatation of the gallbladder, revealed two small concretions in the gallbladder. These concretions contained a fair amount of calcium and cholesterol, some pigment and a large amount of unidentified black substance.

When cholecystectomy was combined with implantation of the cannula, the cannula remained in place in the duct, and incrustations formed on its inner and outer surfaces, but only a small amount of obstruction occurred. The incrustations contained little calcium, a trace of cholesterol and bile pigment and a large amount of unidentified black residue. Local bile stasis and the presence of a foreign body seem to have played a part in their formation.

When bile stasis is produced by inserting a glass cannula into the common duct with a large diverticulum-like attachment, the bile in this "diverticulum" usually remains liquid, and only occasionally are small precipitations found.

CONCLUSION

While it cannot be stated that true gallstones were produced by these experiments, deposits were obtained in the gallbladders and common ducts of dogs which bore some resemblance to calculi.

CAUSE OF DEATH IN CASES OF MECHANICAL INTESTINAL OBSTRUCTION

CONSIDERATION OF CERTAIN CONFUSED ISSUES AND REVIEW OF RECENT LITERATURE

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One who studies the literature on the cause of death in cases of intestinal obstruction finds confusion and conflicting opinions concerning many phases of the problem. This fact was the stimulus for writing this paper, the purpose of which is to consider the experimental studies that have been made since Cooper's review of the subject in 1928 and to present the present status of knowledge concerning the problem. In order to discuss many of the confusing issues, some of the older work will be considered.

In most instances of clinical obstruction and in the various types of experimental obstruction, death occurs before gross perforation of the intestine has taken place, and under these circumstances the cause of death cannot be satisfactorily explained by the autopsy observations. The course has been described as that of "toxemia," and for many years it was generally accepted that the cause of death from all types of obstruction was the absorption of some toxic substance from the gastrointestinal tract. However, recent studies have suggested that different types of obstruction may cause death by different mechanisms.

SIMPLE HIGH INTESTINAL OBSTRUCTION

After a duodenal or a high jejunal obstruction has been made, there is a symptomless period of eighteen to twenty-four hours or longer, and then the picture of the so-called "toxemia of high obstruction" develops. The obstruction prevents the absorption of food and the secretions of the upper part of the intestine, and vomiting is marked. The animals become greatly dehydrated and show tremors and weakness of the hindlegs; the pulse becomes weak and rapid; the blood pressure falls; the urine is scanty, and coma usually precedes death (Cooper). The average period of survival is five days. Obstruction of the duodenum just below the opening of the pancreatic and common bile ducts causes the most acute onset of symptoms and the earliest death.

This paper was written during the tenure of a fellowship in surgery at the Johns Hopkins University and an assistant residency in surgery at the University Hospitals, Iowa City. Dr. Ferdinand C. Lee has made many helpful suggestions.

The periods of survival with lower obstructions are in a general way proportional to their proximity to this point. This was established by Draper, and the point under discussion is often called the "lethal line of Draper." It has been amply confirmed (Dragstedt, Lang and Millet; Dragstedt, Moorhead and Burcky). At autopsy there is "congestion" of all the viscera, but congestion of the duodenal mucosa is particularly prominent. However, there are no pathologic observations that are sufficient in themselves to be the cause of death. Definite alterations in the composition of the blood have been reported by many investigators, and some of these are fairly constant. A fall in the concentration of chlorides, an increase in nonprotein nitrogen and evidence of hemoconcentration are found in all cases of high obstruction (Gamble and Ross; Haden and Orr). There is always some degree of alkalosis with pyloric obstruction, and this is variable if the obstruction is below the pancreatic ducts (McIver).

Death in cases of experimental high obstruction is essentially due to loss of water and sodium chloride and the resultant dehydration.

There is not universal acceptance of this postulate, but it is supported by most recent investigators, largely on the basis of three types of experiments.

1. The lives of dogs with high intestinal obstruction can be prolonged for over three weeks by parenteral injection of sufficient amounts of water and sodium chloride. This was first shown in 1912 by Hartwell and Hoguet and was substantiated by Haden and Orr, who found that under these conditions the blood chemistry remained essentially normal. The loss of fluid cannot be made up by administration of water alone or of solutions of dextrose, sodium bicarbonate, ammonium chloride, calcium chloride or other ions (Foster; Gamble and Ross; Gatch, Trusler and Ayers; Haden and Orr). Physiologic solution of sodium chloride is in general most satisfactory, and concentrated solutions of sodium chloride prevent a marked fall in the blood chlorides but do not significantly prolong survival (Gatch, Trusler and Ayers; Schnohr).

Mechanism of Dehydration. — This was carefully studied by Gamble and Ross, McIver and Gamble, and Atchley and Benedict, and this work was summarized by McIver in 1934. It was noted that losses of sodium and chloride ions were in themselves largely responsible for the dehydration and alkalosis. The volume of a body fluid is sustained by its total ionic content. Quantitatively the chief factors making up the total ionic content of the digestive secretions, blood plasma and intercellular fluids are the sodium and chloride ions. Under the conditions of obstruction a marked depletion of sodium and chloride occurs, and thus a depletion of the total ionic content of the plasma and of the intercellular fluids takes place. This is of necessity accompanied by a

parallel loss of water. In other words, dehydration is regarded as a result of loss of the electrolytes sodium and chloride. In order to restore and sustain the original volume of blood plasma and the intercellular body fluids, there must be replacement of the lost electrolytes. Gamble and Ross substantiated their theory by experiments in which they showed that a large amount of sodium as well as of chloride is lost in the vomitus and that there is definitely a lowering of the sodium content of the serum. In the production of dehydration, loss of the sodium ion is much more significant than loss of the chloride ion. The decrease in the total ionic content caused by loss of the chloride ion is quickly compensated by an increase of bicarbonate ion. There is no comparable mechanism for replacement of the sodium ion.

The alterations in acid-base equilibrium are governed by the proportion in which the sodium and chloride ions are lost. The sum of the acid ions in the plasma must be equivalent to the total of basic ions. Sodium accounts for over 90 per cent of the basic ions. If the quantity of the ions is changed, this equivalence is maintained by the adjustability of the bicarbonate ion. In the presence of pyloric obstruction the chloride ion is lost to a greater extent than is the sodium ion (owing to loss of hydrochloric acid in the vomitus), and the excess of the basic ions (mostly sodium) is covered by an increase in the bicarbonate ion; thus there is alkalosis. In the pancreatic juice and in the bile there is a larger amount of fixed base (sodium) than in the gastric juice, and this increased sodium is balanced by the bicarbonate ion. Therefore, loss of these secretions tends to reduce plasma bicarbonate and to cause acidosis. Thus in the presence of high duodenal or jejunal obstruction the presence or absence of alkalosis or acidosis will vary with the relative loss of gastric juice on the one hand and of bile and pancreatic juice on the other. In the presence of high obstructions the loss of gastric juice is usually greater, and hence alkalosis usually occurs.

The lowering of the level of blood sodium and chloride is adequately explained by the amounts of sodium and chloride recovered in the vomitus (Gamble and Ross; Gatch, Trusler and Ayers; Raine and Perry). The marked electrolyte loss occurs during the early, or "critical," period of obstruction, since it was shown by Foster and Hausler that when dogs with simple high obstruction are given sufficient amounts of physiologic solution of sodium chloride for only the first four or five days they will survive three or four weeks and show no hypochloremia. This has been confirmed by others (Gatch, Trusler and Ayers; Wangensteen and Chunn). There is no definite "lethal level" of blood chloride or sodium. The values found in blood specimens taken just before death vary markedly. McIver stressed the fact that the level of the blood chlorides is not a true measure of the total extent of dehydration of the body. The loss of plasma electrolytes is replaced

from the intercellular fluids, and it has been found that a marked reduction in water content of the subcutaneous tissues and of the skin occurs in cases of high obstruction (Miller). These tissues are abundant sources of intercellular fluids.

2. The survival of animals with high intestinal obstruction has been markedly prolonged by administration of vomitus and dextrose or other solutions containing sodium chloride and food into an enterostomy below the obstruction or by shunting the secretions of the upper part of the intestine below the obstruction. Jenkins and his co-workers have done a number of such experiments. With 2 dogs, survival periods of fifty-two and seventy days respectively were attained by jejunostomy feedings below the obstruction. Similar experiments have been done by several other groups of investigators (Armour and others; Pearse; White and Fender).

3. Animals with high intestinal fistulas die in the same length of time and show the same symptoms and almost the same changes in chemical composition of the blood as do animals with high intestinal obstruction, and their lives may be markedly prolonged by the administration of physiologic solution of sodium chloride. This has been demonstrated by Walters, Kilgore and Bollman and substantiated by others (Dragstedt and Ellis; Morton and Pearse). Morton and Pearse contended that "it is necessary to assume that either there is a toxemia present in both high intestinal obstruction and fistula at the same level, or that there is no toxemia in either."

Objections to the Theory that Death from High Intestinal Obstruction Is Due to Electrolyte Loss and Dehydration. — Investigators have attempted to produce in normal dogs electrolyte loss and dehydration comparable to those found in cases of high intestinal obstruction by gastric lavage and by inducing vomiting with such drugs as pilocarpine. Earlier workers found that dogs could be apparently dehydrated, yet show little evidence of intoxication and quickly recover when given food and water (Ingvaldsen and others). No blood studies or attempts to determine quantitatively the degree of dehydration were made, but recently Taylor and others, using similar methods, obtained blood chloride levels as low as 260 mg. per hundred cubic centimeters and maintained them for several weeks without obvious intoxication. However, it has been noted that the level of blood chloride is not a true measure of dehydration, and hence these experiments can hardly refute the dehydration hypothesis.

LOW INTESTINAL OBSTRUCTION

Experimental low ileal obstruction usually produces a picture quite different from that of high obstruction. Although in some dogs vomiting and other symptoms come on rapidly and simulate high obstruction,

the majority of animals vomit little, remain in apparent good condition for seven, eight or nine days and then often die abruptly. The usual range of survival is from two to fourteen days, but there is wide variation (Eisberg and Draper; Elman and Hartmann; Hartwell and others). Attention has been called to the fact that low ileal obstruction in dogs differs from low ileal obstruction in human beings in that the latter almost always brings on acute symptoms and vomiting, and if obstruction is complete the survival is not likely to exceed a few days (McIver). The autopsy observations do not adequately explain death. The most intensive study of the general picture and blood chemistry in the presence of low ileal obstruction is that of Elman and Hartmann. They found that occasionally some dogs vomited and showed a decrease in blood chlorides, hemoconcentration and evidence of dehydration, but these changes were absent in the majority. Parenteral injection of saline solution did not prolong survival. The last-mentioned finding was in confirmation of the earlier work of Hartwell and his associates. Holt, however, stated the belief that electrolyte loss and dehydration play a more significant role in low ileal obstruction than is generally believed and was able to obtain an average survival time of twelve days in a series of 11 dogs to which adequate amounts of physiologic solution of sodium chloride were given. Elman and Hartmann concluded that "death seems due to a profound peripheral circulatory failure or 'shock' which is quite distinct from the circulatory impairment due to dehydration in the case of high obstruction." Most investigators have expressed the belief that in the presence of low ileal obstruction the absorption of toxic material is the most significant lethal factor, but conclusive proof of this hypothesis has never been attained.

Under what conditions of the intestinal mucosa may a toxic substance be absorbed? The normal intestinal mucosa is impervious to any of the various toxic substances obtained from obstructed intestinal contents (Cooper). Many investigators have contended that toxic absorption does not take place until there are definite microscopic changes in the intestinal mucosa. However, others have stated that the selective absorption of the mucosa may be altered before visible evidence of pathologic alteration has taken place. One approach to this question is to study the histologic changes that take place in the mucosa under the conditions of obstruction. Many of the studies cited in the literature were made when it was generally believed that death from all types of obstruction was due to absorption of toxins and when there was little appreciation of the possibility that electrolyte loss and dehydration per se might cause death in certain instances. The majority of investigators of the earlier group reported marked mucosal changes, with infarction and ulceration in cases of experimental obstruction (Cooper; Van Beuren). However, in most instances no note was made

of the various levels of obstruction. Recently Carlson and Wangensteen studied the histologic structure of the bowel wall from autopsies on 35 dogs with simple obstruction at various levels. They found no evidence that "loss of epithelium is a marked or constant characteristic of simple obstruction and necrosis of the bowel wall did not occur in any of the series." Elman and Hartmann, in their study of ileal obstruction in dogs, reported that death occurred without "demonstrable lesions of the obstructed wall or mucous membrane" in over half of the dogs of their series. Thus recent investigation suggests that death in cases of simple intestinal obstruction may occur without definite microscopic mucosal changes. In cases of high obstruction, in which it is generally believed that death is due to electrolyte loss and dehydration and distention is relieved by vomiting, one might expect that death might well occur before mucosal changes took place. One is tempted to postulate that electrolyte loss and dehydration played a part in causing death in the dogs with low ileal obstruction that did not show mucosal changes. This possibility, although not discussed in the reports of Wangensteen and Carlson and of Elman and Hartmann, undoubtedly occurred to these authors. Holt gave dogs with low ileal obstruction large amounts of physiologic solution of sodium chloride and observed mucosal changes in all the dogs at autopsy. The relation between the intoxication associated with intestinal obstruction and the mucosal changes is not definitely established.

Role of Distention in Low Ileal Obstruction.—Several groups of investigators have measured the intraintestinal pressure during obstructions (Morton; Owings and others; Sperling). In general it has been found that pressures between 4 and 19 cm. of water are found in dogs with low ileal obstruction, and Sperling found similar sustained pressures in clinical cases. In these cases peristalsis caused the pressure to rise to 30 cm. of water. Obstruction of the large bowel caused higher pressures, owing to the fact that the ileocecal sphincter made the colon virtually a closed loop. As obstruction proceeds, fluids and gases collect in the lumen. Whether distention augments or inhibits intestinal secretion is a controversial point (Gatch and Culbertson; Herrin and Meek; Montgomery and Swindt). The intestinal gases are derived from swallowed air and from digestive processes. An active diffusion of gases between the blood and intestinal lumen takes place according to the laws governing gases. Diffusion of oxygen and carbon dioxide from the lumen into the blood takes place, and these gases are replaced by nitrogen, which comes from the blood stream (McIver and others). Practical application of this fact is found in the experiments of Rosenfeld and Fine, who found that the nitrogen in the intestinal lumen could be displaced by breathing pure

oxygen. An increase of the survival period in animal experiments was reported, and encouraging results were obtained in using this method for the clinical treatment of postoperative distention (Fine and others). Hibbard, working in Wangensteen's clinic, made a number of studies of the intestinal gases in the presence of obstruction. He discovered that under the conditions of obstruction gases of the volatile basic group (ammonia, methylamine and tertiary amines) were found. In an earlier report, Hibbard concluded that the volatile basic group of gases were harmless in the concentrations present in obstruction. Later, Hibbard and Kremen reported that a distillate containing the volatile bases and buffered at a specific p_H caused death when injected into closed loops of intestine of a normal dog. However, absorption seems dependent on an optimum p_H, which has not been shown to occur in the presence of an obstructed intestine. Few studies have been made in this respect; hence the role of the volatile gases as a toxic factor cannot be settled at this time.

Effects of Measured Intraintestinal Pressure on Microscopic Appearance and Permeability of the Bowel Wall.—Many ingenious methods of distending the intestine and observing the effects have been carried out. In general, for each increase in intraintestinal pressure there is a corresponding decrease in the volume of blood per minute circulating through the wall (Dragstedt and others; Gatch and Culbertson; Gatch, Owen and Trusler). Sperling distended loops to pressures known to exist in cases of experimental and clinical obstruction (20 cm. for twenty-four hours) and found that necrosis, loss of viability and abnormal permeability of the wall occurred. He noted that viability (as tested by response to faradic current) was lost before the wall became directly permeable to potassium ferrocyanide.

Effect of Distention on Blood and Plasma Volume.—Aird made studies of the blood and plasma volumes in cases of low ileal obstruction and found significant decreases but did not conclude that these were of such proportions that they could be the lethal factor per se. Recently, however, Gender and Fine have reported that average losses of plasma volume of 55 per cent occurred in cases of experimental low ileal obstruction and have postulated that death can be attributed to this decrease of plasma volume per se.

ABSORPTION IN CASES OF INTESTINAL OBSTRUCTION

The possible avenues of absorption of a toxic material are: (1) direct permeation of the wall, usually referred to as "transperitoneal absorption"; (2) absorption through the mesenteric vessels, and (3) absorption through the lymphatics. Absorption in the presence of obstruction has been studied largely by introducing various substances

into the lumen and subsequently testing for their absorption or attempting to demonstrate toxic factors in the body fluids. Many substances have been used, and many methods of testing for their absorption have been devised. Certain generalizations may be made:

1. Transperitoneal absorption of toxic material occurs only through nonviable bowel.

This general statement has been made by a number of investigators (Gatch and Culbertson; Gatch, Owen and Trusler; Sperling and Wangensteen; Wangensteen). These investigators found that certain dyes and potassium ferrocyanide did not pass through the wall until it was nonviable. However, difficulty arises in defining the term "viable." The fact that viability is present as indicated by muscle contractions possibly may not mean that every other physiologic characteristic of the intestine, such as mucosal selectivity, is functioning normally (Jacques and others).

2. There are no experimental results which suggest that absorption of any substance normally absorbed is increased in the presence of obstruction.

On the contrary, there are many reports that the absorption of such substances as calcium iodine, (Clairmont and Ranzi), strychnine (Wangensteen), sodium chloride (Enderlen and Hotz) and phenolsulfonthalein (Palma) is decreased in the presence of obstruction.

3. Is there any experimental proof that under the conditions of intestinal obstruction substances are absorbed that are not absorbed by normal intestine?

Tests have been made for the absorption of such substances as histamine, epinephrine, acetylcholine and collodial graphite. In general, there is no evidence that obstruction allows absorption of these substances (Carlson and others; Dobyns and Dragstedt; Wangensteen and Loucks). However, Haerem, Dack and Dragstedt have recently found that the toxin of Clostridium botulinum could be demonstrated in the blood after being injected into an obstructed loop. In comparable quantities this toxin was not absorbed from the normal dog intestine. They noted that gross necrosis of the distended segments did not always occur when the toxin was demonstrated in the blood stream. This suggested that abnormal absorption, in this instance at least, was not dependent on visible microscopic degenerative changes of the mucosa. In a comparable type of experiment, Hettwer and Hettwer sensitized guinea pigs to horse serum. After injection into an obstructed loop of such a dose as was noneffective when introduced into normal intestine, it was found that absorption occurred, as shown by the anaphylactic reaction which took place. Thus there is some experimental evidence that abnormal absorption occurs in the presence of obstruction, but its correlation with the state of the mucosa is not definite.

4. Lymphatic absorption is increased in cases of intestinal obstruction, and certain substances are absorbed through the lymphatics that are not absorbed by the normal intestine.

Certain dyes and bacteria which are absorbed by the normal intestine have been found in the lymph nodes in various cases of experimental obstruction (Sperling and Wangersteen; Stone and Firor). It is an accepted physiologic principle that increased intraluminal pressure and associated increased mesenteric venous pressure cause increased lymphatic absorption. Some investigators have explained this absorption largely on the basis of stasis and have stated that in normal intestine absorption is prevented by the rapid transit of the material through the bowel. In 1915 Murphy and Brooks recovered toxic material from the thoracic ducts after having injected such material into a loop which was subsequently distended. There are no reports that this interesting experiment has been repeated.

Recovery of Toxic Materials in Body Fluids.—If there is absorption of toxic material in cases of simple obstruction, it would seem plausible that in some manner such material could be recovered from the body fluids. A few such positive claims have been made, but it may be stated that as yet no one has conclusively shown the presence of toxic material in the body fluids in cases of simple obstruction. The entire blood content of toxic animals with various types of obstruction has been transfused into normal animals without effect (Carlson, Lynch and Wangensteen; Foster and Hausler; South and Hardt). A few positive claims have been made concerning the recovery of toxic material from the peritoneal fluid and the lymph (Schonbauer), but these were not confirmed by other workers (Dragstedt and others; Murphy and Brooks; Murphy and Vincent; Traum). Sugito and Scholefield reported the presence of a toxic substance in the mesenteric veins of a closed loop in the terminal stages of obstruction, but their experiments have been criticized from several points of view and have not been further confirmed.

ISOLATED CLOSED LOOPS

If a segment of small intestine is isolated, the ends inverted and the continuity of the intestinal tract is reestablished by anastomosis, the animal will present a picture in a general way similar to that of an obstruction at the level from which the segment was isolated.

This statement was expressed by Cooper and is well substantiated (Bunting and Jones; Dragstedt and others; Murphy and Brooks; Stone and others). However, there are certain variations. Dogs with duodenal loops present a rather consistent clinical picture; the period of survival is fairly constant (between forty-eight and ninety-six hours), and death usually occurs before the loop perforates. At autopsy

splanchnic congestion is prominent, but few observers have reported more marked changes than congestion in the various organs. Short jejunal loops present a picture similar to that of duodenal loops, but perforation more frequently occurs before death ensues. Survival is in a general way directly proportional to the length of the loop, and long jejunal loops are associated with wide variations in survival (Thurston). When long loops are made, death frequently occurs before perforation takes place. Low ileal and colonic loops are often tolerated for weeks with relatively few symptoms (Cooper; Gatch and others; Murphy and Brooks; Whipple; Wilkie). When short loops are made high in the intestine, there are rapid distention and marked anorexia and vomiting. Changes in the blood chemistry are found which are similar to those reported in cases of simple high obstruction (Dragstedt; Haden and Orr). Burget noted that relief of the distention by aspiration relieved the anorexia and vomiting. Dehydration may be a factor in causing death under these circumstances, but definite mucosal changes are observed at autopsy, and life cannot be prolonged by parenteral fluids, because if these are given the loops will soon perforate. When long jejunal loops (over 35 cm.) are made, the animals become weak, lose their appetite, lose weight, become asthenic and often die of distemper (Thurston). The loops are usually greatly distended, but reports vary as to the state of the mucosa. However, most investigators feel that death is due to slow absorption of toxic material.

NATURE AND ORIGIN OF TOXIC SUBSTANCE IN THE INTESTINAL LUMEN

The contents above an obstruction, from isolated closed loops or from strangulated loops, are toxic when injected into a normal animal.

There is little in the literature to suggest that this statement would not be universally accepted. The word "toxic" is often loosely used in the literature and may mean anything from a transient depression of the blood pressure to actual death. The course, symptoms and eventual outcome have varied widely in the hands of different investigators. Crude material obtained from the lumen of the obstructed intestine is almost always toxic and is usually lethal when injected intravenously; when it is injected intraperitoneally it usually causes the same picture, but the effect is more prolonged and peritonitis is a conflicting factor (Habler; Knight). There are many obvious objections to conclusions drawn from this sort of experiment, and most investigators have attempted to obtain a more purified material. Thus filtrates, supernatant fluid from centrifuged specimens and detailed chemical methods have been used to obtain purified products. In general, these have led to more consistent results in the hands of those who have used them, but variations were found in that various investigators isolated materials

that had different chemical and pharmacologic actions. However, the majority of investigators have found that their toxic material was water soluble, heat stable, largely removed by a Berkefeld filter and precipitated by alcohol. The following substances have been reported to have been recovered from toxic obstructed material: choline and neurine (Nesbitt), a heteroproteose (Whipple), a nucleoprotein (Ingvaldsen and his co-workers) and histamine (Gerard). The preponderance of opinion is that the toxic substances which most investigators have found in obstructed contents are either secondary, derived products of protein decomposition (the proteoses) or amines which are formed by bacterial action. Whipple and his various co-workers contended that the toxic material is a heteroproteose and later that it is nucleoprotein but that it is definitely not histamine. On the other hand, Gerard contended that the properties of the obstructed content can be accounted for by their content of free and combined histamine, although he expressed the opinion that other toxins are also present. Gerard recovered significant amounts of histamine from closed intestinal loops. These variations suggest that there may be several toxic substances existing under different conditions.

The crude substance of the various toxic preparations may be introduced into the lumen of the normal small intestine with no untoward results. This postulate was expressed by Cooper and is generally accepted.

The question then obviously presents itself: Are normal intestinal contents toxic when injected intravenously or intraperitoneally? In Cooper's review the general statement was made that they are not toxic or are only slightly so. In reviewing the original papers, the author found that many of the investigators generally referred to as supporting this contention had limited their work and in most instances their conclusions to the secretions of the intestinal mucosa per se (Davis and Stone; Dragstedt and others) or to the toxicity of autolyzed normal mucosa. Much of the early work has been repeated, and the more recent experiments show that both normal and obstructed contents are toxic (Van Beuren; Gatch, Trusler and Lyons; Wangensteen and Chunn), their toxicity depending on the method of preparation of the material and the manner of injection. Gatch and his co-workers have reported that the contents of the higher part of the small intestine are highly toxic and those of the lower part much less so. They have found that the normal combined pancreaticoduodenal secretion is highly toxic and usually lethal when injected into a normal animal. The experiments of other investigators have offered confirmatory evidence concerning the toxicity of the normal pancreaticoduodenal secretion or the activated pancreatic juice (Bottin; Cybulski and Tarchanoff; Sugito; Sweet).

Toxicity of Obstructed Contents.—Although the pancreaticoduodenal secretion may be the primary factor in causing the toxicity of normal intestinal content, there is reason to doubt that it plays the sole role in causing the toxicity of the contents above a low ileal obstruction. These contents are toxic in obstructed dogs from which the pancreas has been previously removed (Ingvaldsen and others). The secretion of the duodenum per se has not been found toxic (Davis and Stone), and there is little to suggest that the other intestinal secretions are very toxic.

Role of Ingested Food.—Hibbard and Kremen have reported that survival of obstructed dogs is decreased if the animals are fed high protein diets. Certain early reports stated that the intestinal contents are highly toxic after diets high in meat and only slightly toxic after diets of only milk (Dobyns and Dragstedt). However, Habler has recently reported that protein-free nourishment did not alter the period of survival. Thus the relation of ingested food to the toxicity of obstructed intestinal contents is obscure, but certain of the intermediary products of digestion are toxic, and there are no experiments which prove that these substances do not make some contribution to the toxicity of obstructed contents, although the general consensus is that their toxicity is of secondary importance.

Bacterial Origin of the Toxin.—Cooper stated in his review in 1928 that "the preponderance of opinion seems to be that bacteria play an essential role in the formation of the toxic substances in obstructed intestinal content." The basic experiments which substantiated this contention were those of Dragstedt and his co-workers, who were able to autosterilize isolated loops by leaving them open in the abdominal cavity. These loops could then be closed or even strangulated without causing symptoms.

Toxicity of Autolyzed Intestine.—If, in any type of obstruction, the circumstances are such that the wall has become nonviable, the subsequent process of autolysis is intensely toxic. Bacteria have been shown to play an essential role in this process. If segments of bowel are excised, washed with the usual antiseptics and returned to the peritoneal cavity, death quickly ensues (Wangensteen and Waldron). It is almost impossible to sterilize segments of intestine by this means (Dragstedt, Moorhead and Burcky; Dragstedt, Dragstedt, McClintock and Chase; Scott). However, Scott sterilized segments in the autoclave, and such segments caused no ill effects when placed in the abdominal cavity. It seems that these experiments offer valid evidence that the toxicity of autolyzing intestine is dependent on bacterial action.

Role of Bacillus Welchii.—Williams in 1926 contended that the absorption of B. welchii toxin is an important factor in causing death

in cases of intestinal obstruction. Although he reported a mortality of 9.5 per cent in a series of cases treated with B. welchii antitoxin, there has been no satisfactory confirmation of the clinical value of the antitoxin in cases of obstruction. Experimentally, the survival of obstructed animals has not been prolonged by the antitoxin (Holt; Owings and McIntosh), and investigators have failed to find immune bodies in the serum of animals with intestinal obstruction (Thurston). The preponderance of recent work shows that there is little evidence that the toxin of B. welchii is the primary factor in intestinal obstruction.

Summary.—The toxicity of normal intestinal contents is largely due to the toxicity of combined pancreaticoduodenal secretions and possibly to some of the intermediary products of digestion. The toxicity of obstructed contents which receive and retain the pancreaticoduodenal secretions may be due primarily to the presence of these combined secretions. However, the toxicity of obstructed contents in cases of low intestinal obstruction is more likely due to histamine, histamine-like substances from bacterial putrefaction or secondary, derived products of protein decomposition. If an obstruction has proceeded to such an extent that the wall is nonviable, the subsequent autolysis is highly toxic. This toxicity is apparently dependent on bacterial action.

STRANGULATION

Death frequently occurs in cases of experimental strangulation before gross perforation occurs. The period of survival is governed by the length of the loop and the type of strangulation. In general, the longer the loop, the shorter the survival (Aird; Foster and Hausler; Wahren). The type of strangulation is more significant than the length of the loop. Thus the following average periods of survival were noted by Scott and Wangensteen for the various types of strangulation that have been studied:

		Length	Hours
Group 1	Encirclement with a rubber band about the mesentery	1 to 5 feet (30 cm. to 1.5 meters)	4
Group 2	Ligation of arteries and veins	1 to 5 feet (30 cm. to 1.5 meters)	20
Group 3	Ligation of arteries alone	1 to 4 feet (30 cm. to 1.2 meters)	20
Group 4	Ligation of veins alone	3 to 5½ feet (91 cm. to 1.6 meters)	5

Composition of Blood.—Death occurs in the absence of dehydration, and there are no marked alterations in the blood chemistry other than a moderate increase in nonprotein nitrogen (Cooke and others; Gatch, Trusler and Ayers).

Significance of Loss of Fluid.—Holt measured the amount of fluid lost in strangulated loops by enclosing them in a rubber bag and con-

cluded that in the long loops enough fluid was lost to cause death per se. Knight and Slome opposed this postulate by stating that if a toxic factor caused death in the short loops it would also be a factor with the longer loops. They objected to Holt's experiments on the basis that the rubber bag prevented reabsorption of the peritoneal fluid. They measured the loss of fluid by weighing the loops and swabbing the peritoneal cavity with cotton swabs of known weight. It was concluded that, regardless of the length of the loop, "there was no constant relations between the amount of fluid lost from the circulation and the survival time." However, Scott used a method similar to that of Knight and Slome and found that in strangulations of two types, encirclement of the mesentery with rubber bands and ligation of the veins alone, the loss of blood itself was sufficient to cause death, but this was not true with the types in which the arteries or both the arteries and the veins were ligated. These studies were based on the postulate of Blalock that a loss of fluid equivalent to 4 per cent of the body weight must occur to cause death from fluid loss alone. Although there is dissension as to the relative role of fluid loss and strangulations, these experiments would lead one to feel that with long loops, at least, the loss of fluid is in itself sufficient to cause death.

Recovery of Toxic Factors in Body Fluids.—If the strangulation is sufficient to shut off the lymphatics and the venous return, it would seem that if absorption of a toxin occurs it must be by means of transperitoneal absorption. Under these conditions one would expect that toxic materials would be present in the peritoneal fluid. However, this has been rather difficult to demonstrate. Scott and Wangensteen injected untreated peritoneal fluid from dogs that had died of strangulation without rupture into normal dogs (intravenously) and found no immediate or delayed effects. In experiments in which the loops had ruptured, there were innumerable bacteria, and the animals died of a generalized gas bacillus infection. On the other hand, Knight and Slome reported that fluid collected by means of a rubber bag placed about a nonviable loop caused a marked and sustained depressor effect on a normal cat's blood pressure and in large doses was lethal. Knight reported that samples of peritoneal fluid from cases of strangulation in human beings caused a "depressor" action when injected in small amounts into anesthetized cats. Some of the samples caused only a transient depressor effect but those from patients with gangrenous segments of intestine caused the blood pressure to remain at a "permanently low level."

Wahren found that fluid from a rubber bag about strangulations in rabbits when injected into a normal rabbit caused a state of shock which was sometimes lethal. Aird and his associates also found such fluid to be toxic.

The period of survival in cases of strangulation of small and medium-sized loops is increased by enclosing the loops in a rubber bag (Foster and Hausler; Holt; Wahren). The usual interpretation is that the rubber bag prevents absorption of toxic material.

Nature of the Toxic Material Collected in Such Rubber Bags.—Wahren reported that histamine, acetylcholine, adenylic acid and other known depressor substances are not present in significant quantities and that it is probable that a markedly toxic substance not yet chemically defined is responsible for the toxic properties of such fluids. Aird reported isolation of two chemical compounds from such fluid that produced toxic effects when injected into normal animals. One appeared to be a protein of the euglobulin class, while the other resembled histamine. Later, Aird and Henderson reported that "the histamine content of the transudate from strangulated loops was exceedingly high but histamine could not be regarded as the sole lethal factor in intestinal strangulation."

Several investigators have called attention to the fact that it is difficult to evaluate the role of substances recovered from such fluid by injecting them into normal animals, because the strangulated animal will have more or less loss of blood volume and perhaps other such factors that would cause lessened resistance (Aird and Henderson; Maycock). Thus Maycock found that the acute depressor effects of such fluid could be accounted for by the amounts of histamine and choline present but that these quantities were not great enough in themselves to produce lasting harmful results. He found that slow intravenous injection of such peritoneal transudates into the normal anesthetized animal whose volume of total circulating fluid has been diminished causes death, while intraperitoneal injection of such peritoneal transudate into unanesthetized animals whose volume of total circulating fluid has been diminished in most instances produced no harmful effect.

Recovery of Toxic Factors from Portal Venous System.—Knight and Slome have reported the recovery of substances which had a marked depressor action from the superior mesenteric vein when the entire small intestine of a cat was strangulated. Knight has recently reported that blood taken from the mesenteric veins of segments of strangulated gangrenous human intestine caused a depressor effect. The nature and significance of these depressor materials is open to question on the basis of the technical details of the experiment (Maycock).

ROLES OF A NEURAL MECHANISM AND SHOCK; PATHOLOGY AND PHYSIOLOGY OF THE SPECIAL ORGANS: ROLE OF HYPERPOTASSEMIA

Burget and Herrin and Meek have presented evidence which suggests that reflexes initiated by distention may play a significant role in

causing the anorexia and vomiting associated with obstruction. Taylor and his associates produced "distention without obstruction" by means of a balloon fastened about a rubber tube. When the distended portion of the intestine was denervated, survival was prolonged. These authors suggested that a neural reflex played a definite role but did not discuss the mechanism. Criticism of these experiments has been made by noting that the pressure to which the balloon was distended (100 mg. of mercury) would certainly cause changes in the bowel wall (Knight and Slome).

Role of Shock in Intestinal Obstruction.—Moon and Morgan have written the most extensive paper on the role of shock in obstruction. They concluded that "intestinal obstruction is one of the many conditions which will produce characteristically the shock syndrome." They reported that study of autopsy material in cases of clinical and experimental obstruction revealed the capillary engorgement that is spoken of as characteristic of shock. They reported an increase in capillary permeability to trypan blue in the terminal phases of intestinal obstruction. These authors did not suggest that the role of shock might differ with the various types of obstruction and that there is reason to believe that the terminal prostration in cases of different types of obstruction may be caused by different mechanisms. Thus Elman and Hartmann stated that in cases of low ileal obstruction "death seems due to a profound peripheral circulatory failure or shock, which is quite distinct from the circulatory impairment due to dehydration in the case of high obstruction."

Elevation of the Nonprotein Nitrogen Content of the Blood and Pathology and Physiology of the Kidneys in Intestinal Obstruction.—An increase in the nonprotein nitrogen content of the blood is associated with all types of obstruction. The values are variable and are not such that they can be considered the cause of death per se. The elevated concentration of nonprotein nitrogen is thought by most recent authors to be secondary to the dehydration which accompanies simple obstruction or to the breakdown of body tissue associated with strangulation. Certain workers have postulated impairment of the kidneys as a result of the action of an absorbed toxin (Brown and others; Fox and his co-workers; McQuarrie and Whipple), and some have found pathologic alteration in the kidneys (Brown and others) and impairment in renal function tests (McQuarrie and Whipple), but the prevalent opinion is that these changes are more likely due to dehydration than to the action of a toxin. This, however, is still a controversial point.

Role of the Liver in Obstruction.—Elman and Cole reported that there was central necrosis in a mild form in nearly all, and to a marked degree in 54 per cent, of a series of dogs with simple loop obstructions.

Similar but more consistent changes were found in cases of strangulation. Hepatic function tests showed slightly decreased values in the toxic stages of obstruction, but the earlier work of Werelius, which supported the contention that death in cases of obstruction is due to insufficiency of the liver, has not been confirmed by others.

Role of Adrenal Glands in Obstruction.—Several workers (Scudder, Zwemer and Whipple; Wohl and others; Zwemer) have been impressed by the consistent cellular changes and lipoid depletion observed in the adrenal cortex after death from experimental and clinical obstruction. Wohl and others found that dogs with high intestinal obstruction which were given adrenal cortical extract lived longer than did control dogs. It is well known that the adrenal cortex is essential for life and that it performs certain functions in the control of electrolyte balance and perhaps of capillary permeability. It is an attractive hypothesis that part of the terminal collapse in cases of obstruction may be due to adrenal cortical insufficiency, but as yet this is only a speculation.

Role of Potassium in Intestinal Obstruction.—Scudder, Zwemer and Truskowski reported that in cases of both simple obstruction and strangulation they had found an elevation of the blood potassium to levels previously shown to be toxic. This led them to conclude that potassium is the toxic factor sought in cases of intestinal obstruction. Scudder and Zwemer found marked hyperpotassemia associated with intestinal fistulas and suggested that hyperpotassemia answers the hypothesis previously cited that there must be a toxin present with both high obstruction and high fistulas or absent with both. There is opposition to these views in the work of Bisgard and his associates, who found that the potassium levels became elevated in about half of their obstructed animals but noted that if potassium is the toxic factor it should be elevated in all instances of obstruction with toxemia. Two strangulation experiments were done, and in neither was an increase in potassium observed.

GENERAL SUMMARY

Attention is called to the fact that different physiologic and pathologic alterations take place under the conditions of different types of intestinal obstruction. The preponderance of evidence suggests that death in cases of high obstruction is due to the loss to the body of the secretions of the upper part of the intestine, the essential constituents being water and sodium chloride. Support for this contention is found in the fact that life can be markedly prolonged by replacement of these substances and only these substances. Experiments in which the intestinal secretions were short circuited around the obstruction substantiate this postulate, as does the fact that high intestinal fistulas cause a similar picture and respond in a similar manner.

In the presence of low intestinal obstruction there is opportunity for reabsorption, and, although dehydration and electrolytic loss may explain death in some instances, these factors do not seem adequate to explain death in the majority of instances. The general consensus is that death occurs as the result of absorption of toxic materials. Many investigators have contended that toxic absorption does not take place until there are definite microscopic changes in the intestinal mucosa. However, others have felt that selective absorption of the mucosa may be altered before visible evidence of pathologic alteration takes place. Recent studies have been reported, indicating that death in cases of low ileal obstruction occurs in the absence of marked changes in the intestinal mucosa. It has been suggested that electrolyte loss and dehydration may have been factors in the instances in which mucosal changes were not evident, although this has not been definitely established. The majority of experiments support the contention that there is no transperitoneal absorption or "direct permeation" of the intestinal wall as long as it is viable. Increased intraintestinal pressure tends to decrease absorption of substances normally absorbed by the intestine and has not been shown to cause absorption of most substances that are not normally absorbed. However, a few recent experiments have shown that increased intraintestinal pressures were associated with abnormal absorption of Cl. botulinum toxin in dogs and of horse serum in guinea pigs. Lymphatic absorption is increased in the presence of obstruction, and certain dyes that are not normally absorbed are absorbed by the lymphatics under the conditions of obstruction. There is no conclusive proof that absorption of a lethally toxic material occurs by this route. In general there is no satisfactorily substantiated evidence of toxic materials in the body fluids in cases of low ileal obstruction. Animals with low ileal obstruction die in a state of "shock." There is a decrease in blood and plasma volume which is certainly of some consequence, but the precise role that these factors play is not definitely known.

Recent experiments have shown that normal intestinal contents may be as toxic as obstructed contents, or more toxic. The normal combined pancreaticoduodenal secretion per se is highly toxic. Although the nature and origin of the toxic material in obstructed contents is not clear, reasons are given for the belief that the pancreaticoduodenal secretions play a secondary role in respect to the toxicity of the material collected above a low obstruction. The preponderance of evidence suggests that the toxicity of this material is dependent on bacterial activity, and, although multiple toxins may be involved, part of the toxicity seems to be caused by the presence of histamine or a closely allied substance.

In strangulations of long loops the preponderance of evidence shows that the fluid loss per se may be great enough to cause death. How-

ever, with short loops and with death occurring before perforation, the fatal issue is probably due to absorption of a toxic material which is formed by the action of bacteria on the nonviable tissues of the intestinal wall. Although some experiments have been cited in which the peritoneal fluid was reported not to be toxic, a number of investigators have found toxic material in the peritoneal transudates. The nature of these transudates and their degree of toxicity have been variable. Histamine and comparable substances have been found in these transudates and cause depressor effects on blood pressure. No one substance has been proved sufficient in itself to cause death.

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ACUTE METASTATIC SPINAL EPIDURAL ABSCESS

REPORT OF TWO CASES WITH RECOVERY FOLLOWING LAMINECTOMY

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As can be appreciated from a review of the literature, the diagnosis, treatment and prognosis of acute metastatic spinal epidural abscess may be divided into two epochs. According to Van Den Berg,[1] the first of these, from the initial report of Morgagni[2] until the end of 1928, was, to say the least, despairing, for of 36 patients whose cases were reported only 1 recovered, a mortality of over 97 per cent. Beginning with 1929, a distinct improvement occurred. Of 35 patients described, 19 survived, a mortality of 46 per cent. Of the 20 patients who recovered, however, 5 had some residual paralysis. Browder and Meyers[3] followed Van Den Berg's paper with a report of 5 cases of acute metastatic spinal epidural abscess, in 1 of which the patient recovered. The condition in this case, however, represented an extension of osteomyelitis of the rib. During December of the same year, Campbell[4] described 4 cases, with but 1 recovery. The patients in Raney's[5] 3 cases reported in 1939 had pneumococcic infections, and, as with all previous acute pneumococcic epidural abscesses, all of them died. Still later in 1939, Bunch and Madden[6] reported 4 cases of acute metastatic spinal epidural abscess, in 3 of which the patients recovered. Only 1 patient, however, regained complete function, the others remaining paraplegic two and eleven years respectively after laminectomy.

Any improvement in the prognosis of this infrequent infection undoubtedly has depended on earlier diagnosis and operative interven-

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1. Van Den Berg, W. J.: Acute Metastatic Spinal Epidural Abscess, California & West. Med. **46**:257 (April) 1937.

2. Morgagni, J. B.: De sedibus et causis morborum, Paris, M. C. Compère, jun., 1823.

3. Browder, J., and Meyers, R.: Infections of the Spinal Epidural Space: An Aspect of Vertebral Osteomyelitis, Am. J. Surg. **37**:4 (July) 1937.

4. Campbell, M. M.: Pyogenic Infections Within the Vertebral Canal, Bull. Neurol. Inst. New York **6**:574 (Dec.) 1937.

5. Raney, R. N.: Acute (Pneumococcic) Metastatic Spinal Epidural Abscess: Report of Three Cases, Bull. Los Angeles Neurol. Soc. **4**:31 (March) 1939.

6. Bunch, G. H., and Madden, L. E.: Acute Epidural Abscess with Compression of the Cord, South. Surgeon **8**:291 (Aug.) 1939.

tion. With few exceptions, every patient with an undiagnosed epidural abscess untreated by operation has died, as have, probably, all patients with epidural abscesses of the acute metastatic type. When the diagnosis is made early, before evidence of paralysis has set in, and laminectomy is performed as soon as possible, the chances of recovery are at least somewhat favorable. On the other hand, if the diagnosis is established after complete paralysis has set in, not only is the prognosis grave but, should laminectomy lead to recovery and relief of pain, residual paralysis almost always persists.

If Van Den Berg's figures are accepted and the 2 cases in the present report are added to those mentioned, some 86 acute metastatic spinal epidural abscesses have been observed, and 26 of the patients have recovered. Seven of those who recovered have had some residual paralysis. The discrepancy in the number of cases reported is no doubt due to the difficulty of separating the acute from the chronic type and the metastatic type from that occurring by extension from a contiguous infection. At all events, the disease continues to be uncommon and the prognosis poor. Inasmuch as the patients in the following 2 cases of acute metastatic spinal epidural abscess were operated on prior to paralysis, with complete recovery, and because the cases illustrate some important features in the diagnosis of the condition, it was believed justifiable to describe them.

REPORT OF CASES

CASE 1.—*Acute metastatic lumbar epidural abscess secondary to a furuncle of the left shoulder; infecting organism, Staphylococcus; laminectomy; drainage of the abscess; recovery.*

J. M. S., a white youth aged 19, was admitted to the Los Angeles County Hospital Nov. 13, 1939, with a history of furunculosis of the left shoulder occurring a month previously. On November 3 he first experienced lumbar pain, which was accentuated by forward movement of the head. Shortly afterward he noticed a radicular pain along the left side of the abdomen and found it necessary to walk bent over toward the affected side. He also discovered that coughing or straining accentuated the pain. He observed no weakness of his extremities and no symptoms referable to the bladder. One physician consulted suspected a perinephritic abscess.

Because at this time he was a member of a Civilian Conservation Corp camp, he was admitted to the Station Hospital, March Field, Calif., on November 11. At this time his temperature was 99.8 F. Rigidity of the neck and pain in the cervical region were noted, as well as pain and tenderness in the lumbar region. The general physical examination disclosed nothing unusual in the heart, lungs or abdomen. Except for a positive Kernig sign, neurologic examination revealed nothing noteworthy. Clear fluid containing 23 lymphocytes per cubic millimeter was obtained on lumbar puncture. A Queckenstedt test was not performed, a notation being made that no manometer was available. After the puncture the patient complained of increased headache and pain in the back. He was then seen by a county health officer at Riverside, Calif., who made a tentative diagnosis of poliomyelitis and advised transfer to the Los Angeles County Hospital. At this time no unusual weakness

or paralysis was described, but the rigidity of the neck and spine was still present, and the Kernig sign was positive. The family and past history were unimportant.

On admission the temperature was 102.4 F., the pulse rate 100 and the respiratory rate 16. The patient was mentally clear but obviously ill. He complained of pain in the left lumbar region and in the left side of the abdomen. Forward movement of the neck produced rigidity in the last 40 degrees of flexion. The Kernig sign was positive. Tenderness was noted in both lumbar regions, particularly on the left. The cranial nerves were intact; the deep reflexes were present, active and equal, and the Babinski sign was negative bilaterally. No sensory loss was noted. At this time the impressions were those of poliomyelitis without paralysis, choriolymphocytic meningitis, osteomyelitis of the lumbar portion of the spine and paravertebral abscess.

The value for hemoglobin on admission was 98 per cent, and the leukocyte count was 24,600 per cubic millimeter of blood, with 72 per cent neutrophils. The Wassermann reaction of the blood was negative. Roentgenograms of the lumbar and thoracic portions of the spine taken on November 16 revealed no destructive lesion. The chest was also essentially normal. A slightly cloudy fluid under 240 mm. of pressure and containing 102 cells per cubic millimeter, 90 per cent of which were lymphocytes, was obtained by puncture at the fourth lumbar interspace. The Pandy reaction was positive, the value for total protein was 170 mg. per hundred cubic centimeters, and the Wassermann reaction was negative. No Queckenstedt test was performed.

On November 19, a lumbar puncture at the level of the third and fourth interspaces returned frank yellow pus which on smear and culture showed staphylococci. A cisternal puncture revealed clear fluid, with 96 cells per cubic millimeter and no organisms. An abscess on the scalp which had developed at this time also yielded staphylococci on culture. Another lumbar puncture on November 20, returned xanthochromic fluid with a strongly positive reaction for globulin. No Queckenstedt test was done. Culture of the fluid produced staphylococci, and a blood culture on November 21 yielded Staphylococcus aureus.

The patient's condition continued to be critical. The leukocyte count was 27,800 per cubic millimeter on November 17 and 24,400 per cubic millimeter on November 21. The impression at this time was that of staphylococcus septicemia with perinephritic abscess, abscesses of the scalp and abscesses of the lumbar muscle or epidural abscesses. Staphylococcus bacteriophage was given in doses of 5 cc. every four hours and increased to 10 and 15 cc. each day until the patient's admission to the neurosurgical service, when its use was discontinued.

The patient was seen in neurologic consultation on November 21, at which time marked tenderness over the third and fourth lumbar segments of the spine was noted, with a positive Kernig sign and some stiffness of the neck as well as pain in the lumbar area on flexion. The impression was that of an epidural abscess in the region of the third lumbar segment, without involvement of the nerves. Neurosurgical consultation was then recommended.

When seen by the resident neurosurgeon, on November 22, the patient appeared ill and toxic. A draining occipital furuncle was noted. Stiffness of the neck was evident, and forward flexion produced pain in the lumbar region. On funduscopic examination the margins of the disks were well outlined except for the nasal margin of the left disk, which was moderately blurred. The veins were overfilled. Otherwise the cranial nerves were intact. Examination of the back disclosed marked tenderness from the second lumbar segment to the sacrum, with some fulness of the paravertebral region bilaterally. No sensory disturbance was noted. Motor power appeared to be intact, but there was so much pain on movement of

the lower extremities that this could not be tested satisfactorily. The impression was that of acute metastatic lumbar epidural abscess.

With the patient under avertin with amylene hydrate and ether anesthesia a lumbar laminectomy was performed on November 23. The second to the fifth lamina inclusive were removed. With exposure of the dura, pockets of thick, yellowish pus were opened from the second to the fifth lumbar segments of the spine, above and below which no evidence of abscess formation was discernible. Penrose drains to the dura were inserted through separate stab wounds on the lateral side of the incision. The wound was then closed with chromic and plain catgut, and the cutaneous incision was loosely closed with interrupted fine black silk sutures. Before this was done, powdered sulfapyridine was placed in the wound. The patient was given a transfusion of 500 cc. of citrated blood.

Because of the history of the lumbar punctures through the involved area and the growth of staphylococci from the last sample of spinal fluid, meningitis was feared as a complication. After the laminectomy the temperature subsided and the patient's general condition was good. Drainage from the operative area continued rather profusely. The drains were removed on the fifth postoperative day. When the skin sutures were taken out on the seventh postoperative day, the edges of the skin separated at the upper portion of the wound, and drainage continued. Sulfapyridine was given until the eleventh postoperative day, when the patient's condition was so much improved that it was no longer indicated.

Although he had some vesical difficulty during the first few days, this subsequently improved and did not recur. His postoperative course was thereafter uneventful, and by the thirty-third postoperative day the wound had approximated except for a few small areas where the epithelial tissue had not closed the gap. During the previous week the patient had been up in a wheel chair.

Films of the chest taken on December 14 showed a few calcified tubercles but no other pathologic change. The patient was discharged from the hospital on January 6, the forty-fourth postoperative day, with no residual paralysis. He has remained well since that time.

Comment.—The importance of the Queckenstedt test is evident in this case, and had it been employed it might have led to earlier diagnosis and operative intervention. The danger of meningitis following the injudicious use of lumbar puncture in such a case is evident. Rosamond [7] and Mixter and Smithwick [8] each reported a case in which recovery followed the development of such a complication. Most authors agree that packing the wound wide open is the preferable method of drainage and that without such drainage reopening of the wound has been necessary. Although in this case such packing was not carried out and closure for that reason probably took place more rapidly, the former method is undoubtedly safer and is preferable. The use of staphylococcus bacteriophage and sulfapyridine therapy may have been helpful, but this factor is difficult to evaluate.

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7. Rosamond, E.: Epidural Abscess Complicated by Staphylococcus Meningitis: Report of Case with Complete Recovery Following Operation, J. Pediat. **1**:230 (Aug.) 1932.

8. Mixter, W. J., and Smithwick, R. H.: Acute Intraspinal Epidural Abscess, New England J. Med. **207**:126 (July 21) 1932.

CASE 2.—*Acute metastatic lumbar epidural abscess secondary to a furuncle of the left cheek; infecting organism, Staph. aureus, hemolytic type; laminectomy; drainage of abscess; recovery.*

K. R., a Syrian boy aged 3½ years, was admitted to the Children's Hospital Dec. 12, 1939, with the history of development of a furuncle of the left cheek about two weeks previously. Some two days later he fell on his back, and he complained rather constantly of pain in the lumbar region thereafter. He was taken to his family physician, who obtained normal-appearing roentgenograms of the lumbar region. About three days prior to hospitalization he complained of pain in his left thigh and knee, which seemed to become progressively worse. He kept his left leg flexed. No difficulty with vesical or rectal control was noted. He seemed rather feverish and irritable.

The family history was unimportant except that his mother had died four hours after his birth. His father was living and well. The patient had had no childhood diseases, and his development as recorded was quite normal.

He was seen in neurosurgical consultation on the evening of December 14. He appeared well developed and well nourished. He weighed 35 pounds (15.9 Kg.). He was irritable and resented being examined. His temperature was 101 F. but had been 104 F. on admission. The pulse rate was 140 and the respiratory rate 24. He was clear mentally but obviously ill. Stiffness of the neck was evident on forward movement of the head. The ear drums were intact, as was the nasal septum. Noticeable on the left cheek was a partially healed furuncle. There was no cervical adenopathy, and nothing unusual was discovered in the heart, lungs or abdomen. The left leg remained flexed, and palpation over the lumbar portion of the spine caused considerable pain. No attempt was made to examine the cranial nerves, but from a superficial investigation nothing unusual was discovered. The Kernig sign was strongly positive bilaterally. Because of his irritable condition and the fact that he had been examined several times previously, a complete neurologic examination was not carried out.

Roentgenograms of the lumbodorsal portion of the spine and of the pelvis, taken on admission, showed no pathologic changes. The value for hemoglobin was 65 per cent; the erythrocytes numbered 3,400,000 and the leukocytes 18,650 per cubic centimeters of blood. The urine gave negative reactions for albumin, sugar and acetone, and microscopically no casts or erythrocytes were seen. Wassermann and Kahn tests of the blood on admission gave negative results, and culture of blood taken on December 14 produced no growth after eleven days.

On the afternoon of December 14, Dr. G. M. Jorgenson attempted a lumbar puncture at the level of the third and fourth lumbar interspaces. No fluid was obtained at the fourth interspace, but when the third was punctured 1 cc. of thick, yellowish pus was liberated by aspiration, which on smear and culture proved to contain Staph. aureus of the hemolytic type. In view of the history, examination and results of lumbar puncture the diagnosis of an acute metastatic lumbar epidural abscess was made, and laminectomy was advised.

With the patient under avertin with amylene hydrate and ether anesthesia a lumbar laminectomy with removal of the first to the fifth lumbar lamina inclusive was performed that evening. Thick, yellowish pus was liberated in pockets along the dura from the first lumbar segment of the spine to the upper part of the sacral region. The dura was not torn. Although it was believed that the epidural abscess might have extended a few laminas higher, because of the patient's condition no additional laminas were removed. Material for culture was taken from the epidural abscess and later yielded Staph. aureus of the hemolytic type.

A large Penrose drain was inserted over the dura and brought out through the lower margin of the wound. The wound was then closed with chromic and plain catgut, and the cutaneous incision was loosely closed with interrupted black silk sutures. Because of the infection, vascularity was more noticeable than usual throughout the procedure. During the operation the child was given a transfusion of 300 cc. of citrated blood.

On December 14 the patient was given 5.2 cc. of a 30 per cent solution of sodium sulfapyridine intramuscularly, and, with the exception of 3 cc. on December 17 and 18, he was given a similar amount daily thereafter until December 19. At this time 7 grains (0.45 Gm.) of sulfapyridine was given four times daily by mouth until December 24, when its use was discontinued. This maintained the level of sulfapyridine between 5 and 8 mg. per hundred centimeters of blood. On December 18 the hemoglobin was 69 per cent; the erythrocyte count was 3,610,000 and the leukocyte count 26,100 per cubic millimeter, with 86 per cent neutrophils. By December 28 the leukocyte count had fallen to 10,800, and by January 3, 1940, to 7,000 per cubic millimeter. At this time the value for hemoglobin was 70 per cent, and the erythrocytes numbered 3,750,000 per cubic millimeter. The patient made a satisfactory recovery without evidence of residual weakness. Because he lived out of the city, he remained in the hospital until the wound closed completely. This occurred on January 24. He has been quite well since that time.

Comment.—Fortunately, when pus was obtained on lumbar puncture, the diagnosis was suspected and confirmed by laminectomy performed as soon as arrangements could be made. The value of such early diagnosis and laminectomy would again seem indicated.

GENERAL COMMENT

Etiology.—It is generally believed that abscesses of the epidural space occur either by extension from a contiguous infection or by metastasis from a distant focus. The larger group, composed of abscesses of hematogenous origin, is more interesting and presents a more difficult problem in diagnosis.

According to Dandy,[9] the fatty and loose areolar tissue filling the epidural space offers a foothold for current hematogenous infections, and the intraspinal location of these tissues makes trauma an important inciting agent in their development. It is generally believed that the metastasis of the infectious variety is to the epidural fat. On the other hand, Browder and Meyers[3] have expressed the view that the hematogenous variety metastasizes to the vertebrae, whence it spreads into the epidural space. The explanation of localization in the epidural space without similar hematogenous involvement elsewhere and the reason for the infrequent occurrence of such epidural abscesses with furunculosis so common are neither easily explained nor easily understood.

9. Dandy, W. E.: Abscesses and Inflammatory Tumors in the Spinal Epidural Space, Arch. Surg. **13**:477 (Oct.) 1926.

The striking feature about the pathologic picture of such an abscess is that it occurs between the dura and the periosteum of the vertebrae and in practically every case posteriorly. This is explained by the fact that, in accordance with Dandy's [9] studies of the anatomy of the epidural space, the dura divides into two halves at the foramen magnum, the inner half acting as the dura proper and the outer half serving as the periosteum of the vertebrae, with the epidural space between the two. Posteriorly, this space consists of a layer of fat, connective tissue and arterial and venous plexuses. This space is present only dorsal to the nerve attachments, because ventrally the dura is everywhere closely applied to the bones of the vertebrae and their ligaments. Below the second sacral bony segment, however, the epidural space surrounds the dura on all sides. The lumbar and thoracic regions are the most common locations for these abscesses, which is explained by the fact that the space is only potential in the cervical area. Below the seventh cervical vertebra the space gradually deepens, attaining a depth of 0.5 to 0.75 cm. below the fourth and eighth dorsal vertebrae, after which it again tapers and becomes shallow below the eleventh thoracic and the second lumbar vertebrae. Over the remaining lumbar vertebrae and the first and second sacral vertebrae, the epidural space attains its greatest depth.

Interestingly, with few exceptions the pyogenic organism associated with spinal epidural infections has been the staphylococcus. Only rarely has the pneumococcus been the infecting organism, and invariably it has proved fatal.[5] A few cases of streptococcic infections have been described, and Raymond and Sicard [10] reported a case of infection with the typhoid bacillus.

Between the two extremes of the acute and chronic forms of the disease there occurs a wide variation in the amount of pus and granulation tissue present. Pus may be found to extend from the lower cervical to the lumbar region with no granulation tissue evident, while, on the other hand, the granuloma may be the only evidence of a chronic infection. The spinal cord is either normal or edematous in appearance. In some instances the cord shows microscopic changes similar to those produced by experimental pressure myelitis. According to Elsberg and Hassin [11] such changes are not merely pressure degeneration but are the result of local obstruction of the circulation of the cord and toxemia.

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10. Raymond, F., and Sicard, J. A.: Épidurite purulente lombaire à bacilles d'Eberthe dans la convalescence d'une fièvre typhoïde; paraplégie; ponction lombaire; laminectomie; guérison, Bull. et mém. Soc. méd. d. hôp. de Paris **22**:860, 1905.

11. Elsberg, A. E.: Surgery of the Spinal Cord, in Nelson Loose Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927, vol. 2, p. 459. Hassin, G. B.: Circumscribed Suppurative (Non-Tuberculous) Peri-Pachymeningitis: Histopathologic Study of a Case, Arch. Neurol. & Psychiat. **20**:110 (July) 1928.

Diagnosis.—Although there is variation in the symptoms depending on the location of the abscess, the history in these cases is rather uniform. Usually the story of some previous infection, often furunculosis, can be obtained, and the lesion may exist at the time of onset of the neurologic symptoms, although in most cases it has subsided. Commonly within the first two weeks but at least during the first two or three months after such an infection, the patient complains of a boring pain in the spine, ordinarily limited to an area corresponding to one or two vertebrae. Usually the pain is constant and is accentuated by coughing, straining or any movement of the spine, and frequently it is associated with local tenderness. Localized swelling may or may not be present. Often the disease assumes the character of a severe toxemia, with noticeable malaise and complaints of chilly sensations, headache, generalized myalgia, feverishness and sweating. The temperature may vary between 101 and 104 F. and soon establishes a septic curve, with morning remissions. There is also leukocytosis, with a polymorphonuclear leukocyte count of 12,000 to 25,000 per cubic millimeter. Often culture of the blood yields bacteria. Neurologic signs become evident during the appearance of these toxic symptoms. A radicular type of pain resulting from involvement of the dorsal nerve roots by the advancing infectious process is a distinctive symptom at this time. Depending on the segmental location of the abscess, these root pains may radiate from the back to the front of the chest, to the front of the abdomen or around the pelvis and down the thighs. The spine and neck become rigid, and flexion of the neck on the chest is painful. Extreme tenderness of the spinous processes over the affected area as well as spasm of the adjacent muscles of the back is elicited on examination. Stiffness of the neck and bilaterally positive Kernig signs are ordinarily noted. When the abscess is in the lumbar region, the Kernig signs are extreme and the cervical stiffness slight.

Such are the early signs, and, if the condition is untreated, either gradual or sudden evidence of involvement of the cord becomes apparent, with paraplegia, sphincteric disturbance and sensory loss. As the abscess advances up the space, an advance of sensory loss and paralysis will be noted. When the abscess is in the lumbar region paraplegia becomes manifest more slowly than when it is in the dorsal area, because at the higher levels pressure is exerted on the cord, while in the lumbar region pressure is exerted on the cauda equina.

Although they admittedly increase the hazards to the patient, lumbar puncture and a Queckenstedt test are essential to confirm the diagnosis. When the abscess is in the lumbar region, the danger of initiating meningitis by means of spinal puncture is obvious. On the other hand, the lumbar space is over 1 cm. in depth and is distended with pus, so

that a routine puncture is apt to enter this space only and evacuate pus. It is generally believed that the danger from a properly performed lumbar puncture is less than that which occurs from a delay in establishing the diagnosis because of fear of producing meningitis. If the possibility of an epidural abscess is unappreciated, a diagnosis of purulent meningitis may be suggested when pus escapes from the needle. A cisternal puncture will dispel any doubt. If the condition is suspected, aspiration should be made on the needle during the puncture. Thoracic epidural abscesess produce early block, and Froin's syndrome is commonly present.

Prognosis and Treatment.—As has been emphasized, almost every patient with an undiagnosed and surgically untreated condition of this kind has died. The prognosis depends on early diagnosis, laminectomy and drainage. When these have been achieved, the chances for recovery appear favorable. If the diagnosis is established after paralysis has occurred, not only is the prognosis grave but, should laminectomy lead to recovery and relief of pain, residual paralysis usually persists. Just how much value the use of bacteriophage may have as an additional therapeutic measure remains controversial. In most cases it seems advisable to employ sulfapyridine.

SUMMARY AND CONCLUSIONS

Two cases of acute metastatic lumbar epidural abscess, with operation before evidence of compression had set in and with complete recovery, are reported.

Abscesses of the epidural space are believed to occur either by extension from a contiguous infection or by metastasis from a distant focus. The larger, more interesting group, that of hematogenous origin, presents a more difficult problem in diagnosis. These abscesses almost always occur posteriorly. This is due to the fact that the epidural space is present only dorsally to the nerve attachments, while ventrally the dura is everywhere closely attached to the bones of the vertebrae and their ligaments. The lumbar and thoracic regions are the most common locations for the abscesses, the epidural space being larger in these areas and only potential in the cervical region. With few exceptions the pyogenic organism associated with these infections is the staphylococcus.

Although there is variation in the symptoms, depending on the location of the abscess, the history is rather uniform. Usually the story of some previous infection, such as furunculosis, can be obtained. Commonly, within the first few weeks following such an infection the patient complains of a boring pain in the spine, accentuated by straining or movement. The disease assumes the character of a toxemia, with fever and hyperleukocytosis. Radicular pain becomes evident; the spine

and neck are rigid, and the Kernig sign is positive. Extreme tenderness of the spinous processes over the affected area as well as spasm of the adjacent back muscles is elicited on examination. Either gradually or suddenly thereafter, evidence of involvement of the cord becomes apparent, with paraplegia, sphincteric disturbance and sensory loss. A lumbar puncture and a Queckenstedt test are essential to confirm the diagnosis. When the infection is in the lumbar region the spinal puncture is apt to evacuate pus, and care must be taken not to initiate meningitis. The thoracic epidural abscesses produce early block, and Froin's syndrome is commonly present.

With few exceptions every patient with an undiagnosed and surgically untreated abscess of this type has died. The prognosis depends largely on early diagnosis, laminectomy and drainage. If these are achieved the chances for recovery at least are hopeful. Should the diagnosis be established after complete paralysis has set in, laminectomy may lead to recovery and relief of pain but seldom leads to return of function of the affected muscles.

A SOLUBLE ROD AS AN AID TO VASCULAR ANASTOMOSIS

AN EXPERIMENTAL STUDY

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The feasibility of suturing severed blood vessels has been established by the "auto-hetero" and devitalized vascular transplant work of Carrel and Guthrie [1] and has been confirmed by others.[2] However, the Carrel-Guthrie technic of end to end anastomosis presents technical difficulties which have discouraged its use except by the surgeon with special training.

It is evident that intravascular thrombosis is the primary factor to be guarded against in vascular anastomosis. Local thrombosis is accelerated by liberation of thromboplastic substance, which, to a large degree, parallels the amount of real trauma to the intima of vessels. The precautions to be observed, therefore, are: 1. Minimize trauma to the vessels, especially to the intima, by delicate handling. 2. Use sutures treated with liquid petrolatum or olive oil (platelets are less apt to stick to oil-soaked sutures),[3] and expose a minimum of the suture material to the blood stream. 3. Minimize constriction of the lumen at the site of suture so that, by Venturi action, an increased number of platelets are not brought in contact with the exposed parts of the sutures.

I have eliminated the three stay sutures and further simplified the technic of Carrel and Guthrie so that I think that it may be applied to relatively small arteries. The technic is based on use of a soluble rod introduced into the lumen of the severed vessel, so that the mechanical form facilitates the proper approximation and suturing of the ends of the vessel, in much the same manner that use of a wooden egg facilitates mending a stocking.

METHOD OF PRODUCING ROD

Soluble rods of various diameters may be prepared, with observance of strict aseptic precautions, as follows: Dextrose is heated slowly to 160 C. The slightly caramelized liquid is poured (or sucked) into sterile rubber tubes ranging in

1. Carrel, A., and Guthrie, C. C.: Surg., Gynec. & Obst. **11**:266, 1906.

2. Klotz, O.; Permar, H. H., and Guthrie, C. C.: Ann. Surg. **78**:305, 1923. Guthrie, C. C.: End-Results of Arterial Restitution with Devitalized Tissue, J. A. M. A. **73**:186-187 (July 19) 1919.

3. Markowitz, J.: Textbook of Experimental Surgery, Baltimore, William Wood & Company, 1937, p. 396.

inside diameter from 2 mm. to 3 mm. The filled tubes are then cut into segments 3 cm. long. These segments are dropped into ether for a few minutes. The rubber softens and swells, permitting the dextrose rod to be slipped out of the rubber mold with ease. The rods are then coated with some substance that will serve to protect the intima from the dehydrating action of the dextrose. Such a substance may be gelatin (3 per cent solution) or an oil which is liquid at body temperature. If gelatin is used, it must be made up in a solvent which is relatively nonsolvent for dextrose. Dodeconyl alcohol serves this purpose.

The rods may be fastened to needles which serve as handles and dipped repeatedly into warm, sterile gelatin solution until a fairly uniform coating of gelatin is obtained. The rods are then fastened by means of the handle of the needle to a sterile cork plate in a vacuum desiccator. A partial vacuum is created. The gelatin coat dries in two to three days.

An alternate and simpler method, more recently used, is to coat the rods with an oil which, in the amounts used (0.02 cc.), probably presents no practical dangers from oil emboli. For this purpose theobroma oil U. S. P. (cocoa butter) is blended with some other fat, with wax or with paraffin (with a higher melting point). Theobroma oil U. S. P. (75 per cent) and paraffin (25 per cent) (by volume) produces a blend which liquefies at body temperature. The rods are dipped into sterile solution once, fastened immediately to a sterile cork plate in a desiccator and stored until used.

TECHNIC OF BLOOD VESSEL SUTURE BY AID OF SOLUBLE ROD

The vessel to be sutured is isolated from the surrounding tissue by packs moistened with warm physiologic solution of sodium chloride. The adventitial coat is stripped back from each end of the artery for a distance of 1 cm. The lumen is washed out with physiologic solution of sodium chloride and then with olive oil.

The continuous suture technic is used. After the first suture is placed but before it is tied, the soluble rod, corresponding in diameter to the lumen of the flaccid vessel, is inserted one-half its length into one end of the artery. As the suture is being drawn tight preparatory to tying, the other end of the artery is worked over the protruding half of the soluble rod. The suture is then tied. The free end of the thread is trimmed off, and the continuous "over and over" suture completes the anastomosis. The continuous sutures are placed 1 mm. apart and 1 mm. or less from the ends of the artery. Mild tension is maintained on the thread during this process in order to prevent the sutures from loosening between each sewing maneuver. The site of the anastomosis is then held lightly between the thumb and the index finger while the proximal clamp is removed. The rod goes into solution in the pulsating blood in one minute or less. The peripheral clamp is then removed, reestablishing the circulation. Some slight oozing of blood from the suture holes and from the area between the sutures occurs immediately on release of the clamps, but this bleeding subsides within a minute or two. Pronounced bleeding caused by two sutures inadvertently placed too far apart may be controlled by addition of a single interrupted suture.

After the oozing has completely stopped, permanent reenforcement is obtained by suturing the arterial sheath securely around the artery at the site of the anastomosis. Fifty-five experiments on 33 dogs were done. Obviously, in developing the technic, failure due to the composition of the rod and failure due to faulty surgical technic must be considered. However, after the technic had been established a high percentage of success was realized.

DESCRIPTION

The following description is based on observations of the last eight consecutive operations performed, using the carotid arteries of dogs ranging from a dog weighing 15 pounds (6.8 Kg.) to a dog weighing 60 pounds (27.2 Kg.). The average weight was 30 pounds (13.6 Kg.). There was one failure (due to an occluding thrombus adherent to the suture line) in the case of a dog weighing 35 pounds (15.9 Kg.). The remaining 7 experiments, or 86.5 per cent, were successful. The examinations consisted of making an exploratory incision under sterile precautions at the site of the anastomosis one week after operation to determine the functional patency of the vessel. A second observation followed from two weeks to a month later, at which time the animal was killed and sections of the artery were taken for histologic study.

OBSERVATIONS AT EXPLORATORY OPERATION

At the site of the anastomosis, that part of the fascial sheath which was sutured around the artery had in every instance become fused to the artery and was highly vascularized. The vessel was patent and functioning as determined by palpation. There were no instances of leakage, hematomas, loose sutures or other evidence of degeneration or breakdown of the conduit. The vessel was pliable at the final examination. When the vessel was opened at postmortem examination, the internal wall was glistening and healthy in appearance. The sutures were covered with a semitransparent glistening membrane continuous with the glistening internal wall of the vessel. There was no evidence of constriction, dilatation or sacculation. In only 1 instance was there a small but organized thrombus, which measured about 0.3 mm. in diameter.

MICROSCOPIC EXAMINATION

The endothelium had proliferated across and covered the sutures and the line of anastomosis. The endothelium was slightly thickened at the site of anastomosis but was essentially normal. There was no evidence of intimal injury caused by the dextrose rod. The silk sutures were encapsulated and surrounded by a few foreign body cells. The muscle fibers of the media injured by the sutures were in the process

of repair or were completely repaired by fibroblastic connective tissue. The adventitial layer had fused to the highly vascularized fascial sheath. Essentially, from the functional standpoint and excepting the encapsulated sutures, the histologic picture was that of an artery which has never been operated on.

COMMENT

Although many failures occurred during the developmental stage of the technic, it is considered significant that once the technic was established, a high percentage of successes was realized. Long term studies were not undertaken, because the work of Carrel and Guthrie [1] adequately established the fact that once the thrombosis at the suture site is eliminated by endothelization of the suture line, the sutured artery is subject to the usual functional history of the rest of the arterial system of the animal.

SUMMARY

A new technic for simplifying vascular anastomosis is described, in which a soluble rod is introduced into the vessel to supply mechanical form and support during the suturing process.

The soluble rod dissolves promptly (in one minute or less) in the blood stream after the circulation is reinstituted.

Directions for preparing and storing these soluble rods are given.

The modified Carrel and Guthrie technic of blood vessel anastomosis with the aid of the soluble rod is described.

Histologic studies reveal no injuries of the intima attributable to the dextrose rod.

It is concluded that the soluble dextrose rod, covered with a thin film of oil or gelatin, is a practical aid in vascular anastomosis.

Dr. A. J. Carlson, of the University of Chicago, and Dr. Willis Potts, of Rush Medical College, gave assistance and crticism in this study. Mr. Edwin Smith assisted in the experimental operations.

ACUTE PANCREATITIS

AN ETIOLOGIC REVIEW AND REPORT OF THIRTY-FIVE CASES

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Sir Thomas Watson (1843), in one of his scholarly lectures, commented: "It may seem a slight to the pancreas to pass it over without noticing the diseases to which it is subject. But really these diseases appear to be but few; and they do not signify their existence by any plain or intelligible signs." In point of occurrence, acute pancreatitis is sufficiently uncommon to suffer from diagnostic imprudence, yet sufficiently common to warrant the utmost diagnostic solicitude. At the Beth Israel Hospital between 1921 and 1939 there have been just over 100,000 admissions. Of this number, 33 were for acute pancreatitis, representing an incidence of 1 in every 3,000. This figure is similar to the incidence reported by other American investigators and roughly corresponds to the records of the Leeds General Infirmary in England, reported by Chamberlain (1927). Acute pancreatitis is undoubtedly, then, a rare but dangerous disease, and the widespread interest in this subject can hardly be explained by the statistical incidence. There is an ever increasing school of thought, however, which believes that acute pancreatitis is more *chatoyant* and perhaps milder and more prevalent, frequently masquerading as biliary colic, indigestion or peptic ulcer. This trend of thought is persuasive, and if the assumption is true it is necessary to discipline carefully the laboratory and diagnostic data and in so doing provide the means for a more consistently correct diagnosis. Sir Archibald Garrod's aphorism (1920) that "the more constantly we bear the pancreas in mind as a possible seat of origin of obscure abdominal troubles the less likely shall we be to overlook its lesions" is especially true of acute pancreatitis.

In this investigation of 35 cases of acute pancreatitis, one of the members of the surgical staff gave me access to his personal records for the histories of 2 patients who were treated surgically elsewhere.

This report has been restricted to those cases in which the diagnosis of acute pancreatitis has been either established or confirmed by operative examination. No cases of manifest chronic pancreatitis or of acute pancreatitis secondary to an unmistakable primary process elsewhere

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have been included. Acute pancreatitis resulting from perforation of a peptic ulcer into the parenchyma of the pancreas has been precluded from this study. Records of pancreatic calculi have also been ruled out. It has been found necessary at times to set up arbitrary standards of classification, but whenever possible the surgeon's note has been adhered to closely.

The diagnostic difficulties associated with this disease are clearly evident in these 35 cases, in which the preoperative diagnosis was found to be correct in 11 per cent of the cases in which it was made without reservation. Acute pancreatitis, however, was considered as an alternative diagnosis in an additional 6 cases, resulting in a partially correct reckoning in 17 per cent. This diagnostic error implies no lack of skill or acumen on the part of the sponsors of these opinions but is rather a reflection on the deceptive nature of the disease and perhaps on the loose liaison between certain clinical principles and helpful laboratory data, namely, determinations of the enzyme content of the blood and of the urine. Of these, estimation of the content of blood amylase and lipase has been recently reemphasized as a valuable, rapid and reliable diagnostic aid when used within its limitations.

This lack of diagnostic uniformity finds ample vindication in the writings of most investigators. Von Schmieden and Sebening (1927), in reviewing 1,510 cases in their collected series, found that a correct diagnosis was made in only 21.8 per cent and a suspected or alternative diagnosis in an additional 17.5 per cent. McWhorter (1932), in reporting 64 cases collected from the records of members of the Chicago Surgical Society, found that a correct diagnosis was made in only 12 per cent. Similarly, more recent authors have found the diagnosis proportionately elusive. Confusion with diseases of the gallbladder was frequent in this series of cases, as well as in the reported observations elsewhere. This is indeed a challenge to diagnostic precision in handling a disease associated with such an appalling mortality and must certainly stimulate interest in all of the complex factors of this perplexing problem.

PATHOGENESIS

The protean manifestations of acute pancreatitis are best explained, at least in part, by the varied factors in the pathogenesis of the disease. Despite the general attention that it has attracted, the nature and cause of this lesion remain doubtful. There exists an extensive experimental and clinical literature concerning the manner of origin of acute pancreatitis, and some believe that operation is only a fairly adequate type of treatment. Dragstedt, Haymond and Ellis (1934) suggested that "it is possible that the limit has been reached in the way of operative procedure, and that a further lowering of the excessive mortality must come from

another direction. The fact that the pancreas is an organ indispensable to life, the fact that it is situated in the upper part of the abdomen in close proximity to the extensive celiac nerve plexus, and the fact that it is in a region where the absorption of toxic chemical products occurs with unusual facility operate to limit the scope of surgical treatment."

Many classifications of acute pancreatitis have been described since the first was proposed by Reginald Fitz in 1889. Before him, Klebs (1870) had recognized acute pancreatitis as a cause of "fulminant death" and stressed its pathologic importance. Claude Bernard (1856) reported the production of experimental acute pancreatitis and the early death of the animals following the injection of bile and olive oil into the pancreatic duct. Rokitansky (1863) carefully recorded the pathologic appearance of acute pancreatitis, and in his textbook on pathology these observations were available to Friedreich (1878), who later published the first well defined and complete description of this disease.

At the turn of the century medical interest seemed focused on diseases of the pancreas. The history and development of knowledge of pancreatitis at that time can be traced in the detailed and comprehensive monographs of Körte (1898), Oser (1898), Mayo-Robson and Moynihan (1903) and Opie (1903). The now famous necropsy of Opie (1901), in which he first described the presence of an impacted stone at the ampulla of Vater and carefully pointed out its relation to acute pancreatitis, is legendary in the annals of medical history. Later, Brocq (1926), in a distinguished paper, divided pancreatitis into two types: (1) noninfected and (2) infected. Acute hemorrhagic, acute edematous and subacute manifestations of the disease were considered types of noninfected pancreatitis. The gangrenous and suppurative manifestations were considered types of infected pancreatitis.

The term pancreatitis is in itself misleading, as the appearance of the pancreas is hardly similar to the gross or microscopic changes characteristic of inflammatory lesions elsewhere in the body. Acute pancreatic necrosis is, indeed, a more accurate and descriptive designation, but time-honored precedent makes it difficult to impeach so well established a term as pancreatitis. In this paper the two terms will be used interchangeably.

ETIOLOGIC CLASSIFICATION

McWhorter (1932) suggested a useful classification of acute pancreatitis on an etiologic basis. With minor modifications this classification has been followed in this investigation.

A. Infectious origin.
   1. Invasion of the pancreas along the lymphatics.
   2. Invasion of the pancreas from the blood stream.
   3. Infection by extension along the pancreatic ducts from the duodenum or from the bile ducts.

4. Infection by direct extension from infected foci.
5. Infection following activation of bacteria and their toxins in the normal gland.
6. Infection by bacterial invasion from adjacent altered viscera.

B. Noninfectious origin.
1. Mechanical or obstructive.
   (*a*) Stone in the common duct or in the ampulla of Vater.
   (*b*) Spasm of the sphincter of Oddi.
   (*c*) Edematous occlusion of the ampulla of Vater.
   (*d*) Metaplasia of the epithelium of the pancreatic duct.
2. Chemical; activated pancreatic ferments resulting from
   (*a*) Reflux of bile.
   (*b*) Reflux of duodenal contents.
   (*c*) Autolysis.
3. Degenerative changes in the pancreas.
   (*a*) Changes secondary to benign or malignant tumors.
   (*b*) Changes resulting from vascular degeneration or hemorrhage.
4. Trauma.

C. A combination of two or more factors.

In following this orderly outline of the factors concerned in the pathogenesis of acute pancreatic necrosis, no attempt has been made to consider them separately or in the order of their importance. In fact, as will be seen by their intimate coexistence, it is often impossible to single out the factors of major significance in an individual case.

A. ACUTE PANCREATITIS OF INFECTIOUS ORIGIN

The influence of bacteria as a likely agent in the production of acute pancreatitis has been supported by considerable clinical and experimental evidence. Evaluation of this evidence, however, is difficult, and conclusions drawn therefrom are consequently dangerous. Von Schmieden and Sebening (1927) found bacteria present in the peritoneal exudate in 103 cases of acute pancreatic necrosis and absent in the peritoneal exudate in 84 similar cases. Cultures of the bile yielded bacteria in 54 cases and were sterile in 40 cases of acute pancreatic necrosis. Rehfuss and Nelson (1935), in reporting a collected series of 4,395 cases of acute and chronic cholecystitis, found bacteria present in the wall of the gallbladder in 60 per cent of 1,306 cases and observed "positive bile cultures" in 30 per cent of 1,249 cases. Yet, despite the evident presence of bacteria in the biliary tract in these cases of cholecystitis, associated acute pancreatitis was not noted. Truhart (1902) found bacteria present in the peritoneal fluid, the parenchyma of the pancreas or the foci of fat necroses in 37 of 80 collected cases of acute pancreatitis. In the remaining 43 cases all cultures were sterile. However, bacteria have been shown to be present in the uncontaminated pancreas of the normal experimental animal, and it is likely that a similar situation may exist in man. Tower (1926) found

positive bacterial cultures in 15 of 16 pancreatic biopsy specimens from normal dogs. Bacteria were also regularly observed at autopsy in the peritoneal cavities of dogs subsequent to ligation of the blood vessels supplying the pancreas. These results have been substantiated by Dragstedt (1934) in a group of similar experiments, and he noted, rather surprisingly, that "all cultures taken from the necrosing pancreatic tissue of the dogs that died from autolysis of the pancreas yielded an organism very similar to, if not identical with, Cl. welchii." The predominance of this organism is not corroborated by the bacteriologic studies made in the operating room or at necropsy but, as has been suggested by Dragstedt, may be accounted for by its capacity to overgrow other organisms.

Careful bacteriologic studies of acute pancreatic necrosis are singularly meager, but in those reported colon bacilli, staphylococci and streptococci have been the organisms most frequently cultured. Perhaps the anaerobic bacteria are seldom found because seldom looked for, but even the prevalent Clostridium welchii, when specifically sought, is rarely cultured in cases of this disease.

In the series reported in this paper it is interesting to note that in case 35 there was a growth of hemolytic Staphylococcus albus in all of four separate cultures, the material for which was taken at operation from the gallbladder bile, the wall of the gallbladder, the common duct bile and (by aspiration) the pancreas. Bacterial stains of material from a cystic lymph node revealed no bacteria. The patient showed no postoperative evidence of infection or suppuration and had a rather uncomplicated convalescence. The remainder of the cases were not routinely investigated, and the sporadic cultures that were made were for the most part sterile.

Flexner (1900) carried out a large group of successful experiments in which he was able to produce hemorrhagic lesions in the pancreas by injecting, among other things, bacterial suspensions directly into the pancreatic duct. Hlava (1898) demonstrated a similar lesion but concluded that the hemorrhage and necrosis were not primarily the result of bacterial action.

Bacterial invasion of the pancreas along the lymphatics was first suggested by Klippel and Lefas (1899) as a likely cause of acute pancreatic necrosis. Maugeret (1908) devoted her thesis for the doctorate of medicine to the subject and attempted to produce experimental, clinical and anatomic evidence in support of this mode of pathogenesis. The work of earlier investigators, Sappey (1885), Hoggan (1880), Cuneo (1903) and others, had demonstrated the free lymphatic communication between the biliary tract and the pancreas. Franke (1911), by injecting the lymphatics of the gallbladder with dyes, was able to trace their course to the celiac lymph glands and the lymph channels about the head

of the pancreas. However, he did not demonstrate that the injected material entered the substance of the pancreas. The concept of the lymphogenous route of infection by extension from the gallbladder to the pancreas was given authoritative credence by Deaver (1921), Judd (1921), Arnsperger (1911) and, for a time, Graham (1922). From the experimental indications of the work of Kodama (1926), Graham (1928) modified his earlier conclusions to conform with the evidence that there is no direct lymphatic communication between the gallbladder and the parenchyma of the pancreas. Clinically Deaver (1921) frequently found in his cases of disease of the gallbladder peripancreatitis with associated lymphangitis and lymphadenitis of the pancreas.

More recently, however, Kaufmann (1927) and Wangensteen (1931) have given convincing and rather conclusive evidence that acute pancreatitis is not propagated from the gallbladder to the pancreas through the lymphatics. Wangensteen (1931) was unable to produce acute pancreatitis in dogs by the germination of an acute biliary tract infection. Even direct injection of bacteria into the parenchyma of the pancreas failed to result in acute pancreatitis. Kaufmann (1927) demonstrated that after an acute infection of the gallbladder produced in experimental animals it was not uncommon to find bacteria present in the pancreas, but bacteria could also be found as a result of bacteremia in the tissues of most of the organs of the body. No pathologic evidence to suggest the presence of acute pancreatic necrosis was found in the animals.

Clinically acute pancreatitis seldom follows fulminant hyperacute cholecystitis but is more commonly associated with chronic cholecystitis. Yet, if the lymphatic spread of infection from the gallbladder is of singular significance in the causation of acute pancreatitis, one would expect to find the acute phase of these diseases a concomitant occurrence of far greater frequency.

Bacterial invasion of the pancreas from the blood stream may produce acute pancreatic necrosis on rare occasions, either by metastatic foci in the presence of pyemia or by extension of infectious thrombophlebitis. Experimentally, Rosenow (1921) found that streptococci isolated from the tonsillar crypts of patients who were suffering from disease of the biliary tract had an elective affinity for the gallbladder and pancreas when intravenously injected into animals. Streptococci of unrelated strains showed no such localization. Kaufmann (1927), however, injected bacteria directly into the portal vein and found that a generalized bacteremia resulted in which the organisms could be isolated from the pancreas and from almost all of the other body tissues as well. Microscopic sections of the pancreas revealed low grade perivascular round cell infiltration.

Blood-borne metastatic lesions complicating mumps have been observed by investigators for many years. Brahdy and Scheffer (1931) reported 156 cases of clinically suggestive acute pancreatitis untreated by operation in 8,306 cases of epidemic parotitis. Patients with mumps most often exemplify the acute edematous type of pancreatitis, and the transient attack may be of minor significance. Two reported autopsies confirmed the association of acute pancreatitis and mumps, and an edematous, congested and enlarged pancreas was observed in both cases. In 1 of them the pancreatitis was a contributory factor to acute nephritis and pulmonary congestion. Farnam (1922) reported a case of acute pancreatitis following mumps in which the condition was treated surgically. Streptococcus viridans was isolated from the peritoneal exudate. Hematogenous acute pancreatitis secondary to an acute infectious disease, such as typhoid fever, scarlet fever or diphtheria, is a rare complication and usually results in suppurative pancreatitis. The clinical character of this type of pancreatic lesion is frequently less severe than that of the hemorrhagic or the necrotic type, and the prognosis is distinctly more hopeful. Acute pancreatitis resulting from bacterial invasion by an infective thrombus or from lodgment of an embolus is most infrequent, but when it is recognized the pancreas is found to be the site of either single or multiple abscesses. Douglas (1935) discussed a case of multiple pancreatic abscesses following suppurative portal phlebitis but noted absence of the clinical signs and symptoms suggestive of acute pancreatitis.

In a careful examination of the 35 case histories presented in this report only 3 patients were found to have had an infection of the upper respiratory tract immediately prior to the onset of acute pancreatitis. No further evidence to incriminate the more obvious foci of infection could be uncovered from these records or from the protocols of other investigators.

A history of alcoholism, acute or chronic, was either not mentioned or not present in the records of all of the cases in this series. Weiner and Tennant (1938), in reviewing 4,000 autopsies performed at the New Haven Hospital, found acute pancreatitis in 66 per cent of 38 cases associated with alcoholism, and, conversely, in 53 per cent of the cases of acute alcoholism this condition was associated with acute pancreatitis. The mode of action of alcohol in its relation to acute pancreatitis remains speculative; however, the authors mentioned several interesting physiologic considerations. The role of alcohol alone must certainly be a most insignificant one, considering the almost universal use of this substance, yet the association of alcohol with one or more ancillary factors probably serves as a positive etiologic agent in a limited group of cases in which acute pancreatic necrosis develops.

Bacterial extension along the pancreatic ducts from either the duodenum or the bile ducts has often been shown experimentally to be an inciting agent in the causation of acute pancreatitis. Egdahl (1907) noted clinically that in 32 of 105 cases of acute pancreatitis there were associated gastrointestinal disturbances which could be directly invoked in a causal relation. Alcoholic duodenitis was said to be present in 17 of these cases. It is rather difficult to determine the manner of origin of these pancreatic lesions, although it has been suggested that they occur either by penetration of altered duodenal contents into the pancreatic ducts or by direct extension through the intestinal wall. Hess (1905) suggested that antiperistaltic movements of the intestine, which are frequently associated with enteritis, may aid in forcing gastric or duodenal contents into the pancreatic ducts. Anatomic evidence fails to support this point of view. Regurgitation of duodenal contents is prevented by the oblique, valvelike entrance of the ampulla of Vater, which under increased intraduodenal pressure serves to close the ampulla more effectively and prevent reflux. It is true, however, that an anomalous or patulous papilla of Vater can produce a functional change sufficient to explain the occurrence of acute pancreatitis in rare cases. Most experimental attempts to allure duodenal contents into the pancreatic ducts have been unsuccessful. Seidel (1910) established low duodenal obstruction followed by stasis, regurgitation and so-called acute pancreatic necrosis, but Dragstedt (1934) has challenged the evidence obtained in this experiment as incorrectly interpreted.

Von Schmieden and Sebening (1927) have collected 50 cases of invasion of the duct of Wirsung by ascarides with resultant acute pancreatic necrosis. This demonstration of the penetration of duodenal contents in the form of a round worm into the pancreatic duct is virtually self-evident proof that in certain cases acute pancreatic necrosis may be attributed to infection and irritation by this route.

Direct extension from infected foci has been held responsible for many lesions of the pancreas. In innumerable cases so-called acute pancreatitis has been reported as resulting from penetration of a duodenal ulcer into the pancreatic parenchyma. The pathologic mechanism of this process remains obscure, yet it is confidently regarded by some as a contiguous spread of infection from the adjacent gastrointestinal tract.

The activation of bacteria thought to be normally present in the pancreas has been given but passing consideration as a likely cause of acute pancreatitis. However, Andrews, Rewbridge and Hrdina (1931) offered some vindication for this idea by investigating the role of Cl. welchii in producing intraperitoneal inflammatory lesions. Using dogs, they concluded that the action of bile presumably aids in permitting local tissue permeability by Cl. welchii. This organism has also been

shown to produce a powerful hemolysin, but there is no present evidence to relate this toxin to the hemorrhage and necrosis associated with acute pancreatitis. The presence of bacteria within the parenchyma of the pancreas may yet prove to be an important factor in the pathogenesis of this disease. Dragstedt (1934) and his associates have demonstrated the role of bacteria in enhancing the proteolytic power of the enzyme trypsin. The split protein end products of this reaction, liberated within the pancreas and readily absorbed, may be directly responsible for the marked degree of toxemia exhibited by patients with acute pancreatitis.

Bacterial permeability of an inflamed hollow viscus may occur late in the disease, even without perforation. This has been demonstrated clinically in cases of typhoid fever with resultant localized or generalized peritonitis. Should the peritoneal inflammation occur in the region of the pancreas, fulminant acute pancreatitis may terminally confuse and "climax" such a disease. McClure (1907), however, was unable to confirm the results of earlier investigators regarding bacterial permeability in cases of acute intestinal obstruction. He found that permeability occurs, if at all, very late in the course of mechanical ileus and thus can hardly be the source of a pancreatic infection.

B. ACUTE PANCREATITIS OF NONINFECTIOUS ORIGIN

The theory of mechanical obstruction in the ampulla of Vater, resulting in a common channel between the ductus choledochus and the main pancreatic duct, was first verified as a cause of acute pancreatitis by Opie (1901). The mechanism of the reflux of bile into the pancreatic duct through the agency of an impacted gallstone in the ampulla of Vater is directly dependent on several fundamental considerations. First, the anatomic junction of the ducts at their entrance into the papilla of Vater must be so arranged as to allow their conversion into a functioning common channel by the presence of any one of the following: (1) a small calculus, (2) biliary dyskinesia or (3) acute edema of the ampulla of Vater. Second, granted the formation of a common channel, it is necessary to learn the relative ductal pressures to determine competently in which direction the secretions will flow.

To ascertain these facts, Opie (1903) measured the diverticulum of Vater in 100 specimens and found 89 instances in which the two ducts joined to form a common opening. Of these, there were 30 in which the length of the diverticulum was greater than 0.5 cm. and 21 in which the diameter of the diverticulum was greater than its length, thus making partial occlusion of the orifice by a spherical stone obviously impossible. Baldwin (1911) observed a common entrance of the ducts in 78 per cent of 90 cases, and Ruge (1908) observed it in 75 per cent of 43 cases, but Mann and Giordano (1923), working with 200 fixed

specimens, concluded that in only 3.5 per cent of the cases did the junction of the ducts permit development of a common channel by obstruction at the papilla. Cameron and Noble (1924), however, introduced a small biliary stone into the ampulla of Vater in fresh autopsy specimens and, by forcing fluid into the hepatic duct at a low pressure, noted that a reflux of bile into the pancreatic duct can anatomically occur in 66 per cent of normal specimens.

The literature records more than a few cases of acute pancreatitis in which either the ducts had a separate duodenal opening or the duct of Santorini drained the major portion of the gland. Under such circumstances the theory of the common channel offers no causal solution for acute pancreatitis, and other factors must best explain the pathogenesis in these cases. Thus, although evidence regarding the anatomic plausibility of the theory of a common channel is conflicting, it is probable that in about half of all normal persons the morphologic structure of the biliary tract is such that a small gallstone might divert the bile into the pancreatic duct.

Archibald (1919) has experimentally supported the belief that biliary dyskinesia may convert the ducts into a common channel and that the sphincter of Oddi can withstand a pressure sufficient to allow reflux of bile into the pancreatic duct. Animals under anesthesia were used in his work, but, more recently, confirmatory clinical evidence has accumulated to substantiate this visceral neuromuscular imbalance in man. Wangensteen (1931) and his associates, using cats, mechanically closed the ampulla of Vater with a suture and noted the reflux of bile into the pancreatic duct by contraction of the gallbladder. This produced acute pancreatitis in 50 per cent of the animals. However, they were unable to demonstrate any retrojection of bile without a mechanical obstruction at the papilla. Wangensteen then concluded that the "possibility for such a reflux, however, obtains in a large percentage of persons, and it is possible that such a reflux may be conditioned through a disturbance in the sphincter-regulating mechanism at the ampulla. The actual occurrence of pancreatic necrosis through such an agency in man, however, remains to be demonstrated."

Reflux into the duct of Wirsung has recently been shown to occur during cholangiographic procedures in about 25 per cent of the cases. This is not dependent on a stone at the ampulla but probably more often is due to spasm of the sphincter of Oddi. Yet Boyden (1937) has offered substantial anatomic evidence to show that closure of the pancreatic duct is accomplished primarily through the layer of circular muscle which is common to both bile and pancreatic ducts. The production of a common channel by spasm of the sphincter of Oddi would thus appear to be anatomically improbable even if physiologically possible. An apparent common channel was clinically demonstrated in

case 9 of the present series, in which a bile-stained pancreas was observed at operation. A biopsy specimen taken at the time failed to reveal biliary constituents within the pancreas.

In 1903 Weiner suggested that edema of the ampulla of Vater might so deform its natural structure as to produce a common channel for pancreatic retrojection. Balo and Ballon (1929) supported the possibility of such an occurrence and suggested that it might exist in association with acute or chronic disease of the biliary tract. In their examination of autopsy material they noted evidence of pancreatic retention due to obstruction at the ampulla of Vater. This obstruction was the result of the traumatic passage of a stone associated with an edematous occlusion or a late stricture or possibly the result of a localized inflammation. In a group of unpublished studies on serum amylase which is now in progress I have been able tentatively to confirm this evidence of edematous obstruction and have correlated the results with operative or postmortem observations whenever possible. The presence of a T tube draining the choledochus or the passage of a stone can so impinge on the pancreatic duct or (by edema) occlude it that the altered level of serum amylase will reflect the amount of obstruction of the pancreatic duct.

Should the anatomic arrangement be such as to permit a common channel between the bile and pancreatic ducts, the direction of the secretory flow would, at least theoretically, depend on the individual intraductal pressures. Wolfer (1931) demonstrated that the secretory pressure of the pancreas is greater than that of the liver and gallbladder. This relation has been confirmed by Dragstedt (1934) and his associates. However, Dragstedt concluded that the free intraglandular anastomoses between the ducts of Wirsung and Santorini, as demonstrated by Opie (1903), "make the secretory pressure of the pancreas ineffectual in the majority of cases." The presence of bile and gallstones in the dilated pancreatic duct in a case of acute pancreatitis reported by Robins (1936) corroborates the data in case 9 of the present series and would appear to establish the clinical possibility of the occurrence of pancreatic reflux.

In a facile and instructive study, Rich and Duff (1936), believing that the cause of acute pancreatic necrosis could be found intrinsically within the pancreas, carefully examined the microscopic sections of 150 consecutive autopsies. Metaplasia of the pancreatic ducts was observed in 28.6 per cent of the routine sections examined. In cases of acute pancreatic necrosis, however, the routine sections yielded manifest ductal metaplasia in 55 per cent of the cases. From this it was contended that metaplasia of the pancreatic ducts could cause their secretory obstruction resulting, in turn, in a back pressure rupture of the ductal-acinar system of the pancreas. Trypsin, thus liberated

within the parenchyma of the gland, would then proceed to necrose the surrounding tissue and vessel walls and, by enzymatic destruction, cause acute hemorrhagic pancreatitis. The activation of trypsinogen to trypsin was felt to be unnecessary, as similar vascular necroses could be experimentally produced by injection of purified trypsin.

Yotuyanagi (1937), on the contrary, in an exhaustive study of pancreatic metaplasia, found that it occurred normally in the human being in at least 64 per cent of the specimens which he examined. The metaplasia was a genuine epithelial proliferation, and he suggested a causal relation to vitamin A deficiency or, perhaps, local ductal stasis and irritation. This conspicuous frequency of ductal metaplasia in the normal pancreas is inconsistent with the infrequency of acute pancreatic necrosis and would appear to conflict with the major premise of Rich and Duff.

TABLE 1—*Reported Incidence of Disease of the Biliary Tract Associated with Acute Pancreatitis*

	Cases of Acute Pancreatitis	Associated Chronic Cholecystitis, per Cent	Associated Acute Cholecystitis, per Cent	Associated Cholelithiasis, per Cent	Associated Choledocholithiasis, per Cent	Associated Ampullary Stones, per Cent	Normal Gallbladder, per Cent
Schmieden and Sebening (1927)	Collected, 1,278; personal, 88	..	..	Collected, 70; personal, 81	Collected, 13.6; personal, 40	Collected, 4.4; personal, 20	..
Guleke (1924)	437	..	..	59	5	1.4	..
Egdahl (1907)	105	..	..	42	..	..	..
Fallis and Plain (1939)	26	57.7	15.4	60	8	4	26.9
McWhorter (1932)	64	33	22	40	8	3	29
Present series	35	70	3	80	9	3	20

The importance of the reflux theory of the causation of acute pancreatitis is amplified by a consideration of the relation between chronic cholecystitis, cholelithiasis and acute pancreatitis. Many years ago Körte (1898), Oser (1898) and Opie (1903) all called attention to the frequent association of acute pancreatitis with chronic disease of the gallbladder. Table 1, showing the statistical frequency as collected from the literature, probably represents a certain underestimation, as the contents of the gallbladder and the biliary tract were doubtless overlooked in many instances. These figures are so striking in bearing out the fact that the pathogenesis of acute pancreatitis is intimately related to biliary tract disease that additional clinical corroboration is scarcely needed. In case 15 of the present series the gallbladder was removed eleven years before the development of acute pancreatic necrosis, yet it is difficult to be certain that the pancreatic lesion was not a residue

of earlier cholecystitis. Many similar instances of persistent disease of the biliary tract have been reported in the literature. As Wangensteen (1931) has pointed out, the common denominator in the pathogenesis of acute pancreatic necrosis is the overwhelming preponderance of associated disease of the biliary tract. Whether the mechanism of disease of the gallbladder predisposes to pancreatitis by way of infection, reflux of bile or both remains uncertain, but these facts must now be considered in the light of newer experimental evidence ascribing importance to enzymatic autolysis of the pancreas.

Experiments repeated over a period of many years by many investigators have shown that a great variety of irritating substances will cause acute pancreatic necrosis when injected into the pancreatic duct. The injection of bland substances, as was shown by Flexner and Pearce (1901) and Guleke (1904 and 1908) will not produce such necrosis. The careful work of Flexner (1906) demonstrated that the power of bile to cause pancreatic lesions is attributable to the cytolytic properties of sodium taurocholate and other bile salts. Diverting bile into the pancreatic duct is not only capable of producing glandular necrosis, but, as was demonstrated by Archibald (1929) and others, it is capable of producing intense edema of the gland, which may or may not be the initial stage of a more extensive and fulminant process. Archibald, confirming the earlier work of Nordmann (1913), showed that injection of infected bile produces acute pancreatic necrosis much more consistently than does injection of sterile bile.

Pólya (1912) and others found that injection of active trypsin into the pancreatic duct precipitated acute pancreatitis in practically every experimental attempt. The conclusions drawn were obviously those relating acute pancreatic necrosis to the proteolytic action of trypsin. Criticism of this point of view has been expressed by Mann and Giordano (1923), Sailer and Speese (1908) and McCaughan (1934), all of whom expressed the belief that moderate amounts of any highly irritating fluid injected into the duct under pressure would distend, traumatize and rupture the ductal-acinar system, favoring the development of acute pancreatitis.

The exact relation of the pancreatic enzymes to the necrosis, hemorrhage and destruction of the gland incident to acute pancreatitis is at present a problem. Wangensteen and his colleagues (1931), Rich and Duff (1936) and Brocq and Morel (1919) observed clinically and experimentally that acute pancreatitis usually develops at the height of digestion, and they suggested that increased intraductal pressure associated with acinar rupture probably liberates and activates trypsin, which, in turn, is the essential factor in producing pancreatic necrosis. Dragstedt (1934) and his associates, in a group of ingenious experiments, showed that this particular belief is untenable. Dragstedt has

expressed the opinion that the destruction of the pancreas is primarily the result of the toxic and cytolytic action of the bile salts, aided, to be sure, by trypsin, which removes and digests away the surrounding protective proteins. This was neatly demonstrated in part by a series of window implant experiments, the living pancreas being exposed to the digestant action of duodenal contents in one group of animals and to the action of gallbladder bile in another. Acute pancreatic necrosis regularly developed in the latter group only.

Typical cases of acute pancreatitis with fat necrosis and pancreatic destruction may result from a traumatic injury to the abdomen or from degenerative vascular changes in the pancreas. Pancreatic cysts or neoplasms, by their slow growth and compression of the pancreatic ducts, usually cause atrophy and fibrosis of the secretory acini rather than acute pancreatitis, although this is not always so. Case 6 of the present series clearly demonstrates the production of traumatic pancreatitis. A child 7 years of age was struck by the fender of a passing automobile. Minor external contusions were noted at the time of admission to the hospital, and at operation, three days later, the pancreas was found to be engorged and hemorrhagic, with numerous areas of fat necrosis.

In summarizing the factors of importance which play a role in the production of acute pancreatitis, it becomes necessary at times to consider a combination of several factors, none of which acting individually is capable of producing this disease. Thus, the variable and inconstant results of experimental and clinical bacteriologic studies readily indicate that infection alone is rarely a cardinal factor in the causation of acute pancreatitis but is rather a factor of secondary ingress and activity preying on already injured pancreatic tissue. Anatomic and functional observations in the laboratory and the operating room, although conflicting in certain respects, appear to be in general accord with the evidence favoring the reflux of bile into the pancreatic duct as an important primary etiologic agent. The potent necrosing action of bile, the concomitant frequency of acute pancreatitis with disease of the biliary tract and stones and the digestant enzymatic power of the external secretion of the pancreas substantially endorse the common channel theory and the toxic action of bile in producing the disease.

In those cases in which the role of infection, bile or enzyme activity has been relegated to a place of minor import, other factors of pathogenesis, such as vascular injury, trauma or degenerative neoplastic changes, must be considered as a likely cause of acute pancreatic destruction. Dragstedt (1934), in a critical analysis of the subject, stated that "undoubted cases have been reported in which each one of these factors has operated to produce an entirely characteristic picture of the disease. Likewise, it has been possible to reproduce the disease in the experimental animal by practically any method that insures a sudden and

fairly extensive necrosis of the pancreatic parenchyma." It must be concluded, therefore, that the solution to the problem of the cause of acute pancreatitis is not yet available, although it is apparent that not one but a combination and interplay of many factors may be responsible for this perplexing disease.

PATHOLOGIC PICTURE

The appearance of the pancreas varies most often in accordance with four principal pathologic types of the disease observed either at operation or at necropsy. The aspect of the gland at the time of examination may or may not represent a transient phase in the development of pancreatitis. At present there is considerable uncertainty whether the milder types of this lesion merely represent earlier and less severe degrees of an orderly glandular destruction or whether they are distinct yet related pathologic entities. Quick (1932) called attention to a case in which he found edematous pancreatitis at operation and observed extensive pancreatic necrosis at autopsy two days later. Nevertheless, for the purpose of uniform nomenclature it is well to classify the four types as follows, regardless of the overlapping which probably occurs in most cases:

Type 1. Acute pancreatic edema, with or without fat necrosis.

Type 2. Acute hemorrhagic pancreatitis, with or without fat necrosis.

Type 3. Acute gangrenous or necrotic pancreatitis, with or without fat necrosis.

Type 4. Acute suppurative pancreatitis, with or without fat necrosis.

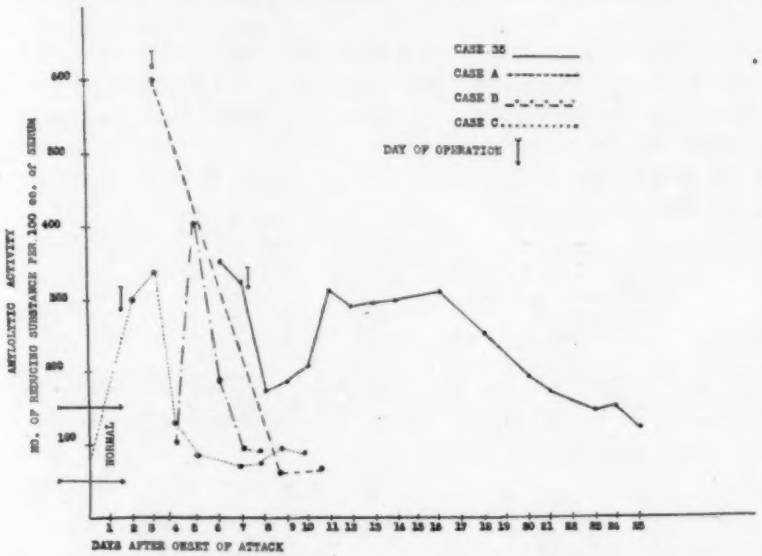
In 2 cases (10 and 12) of the present series the postmortem observations illustrated the essential characteristics of pancreatic hemorrhage and necrosis as observed with types 2 and 3. There were widespread areas of softening and necrosis of pancreatic parenchyma associated with a lesser amount of hemorrhage and surrounded by a small zone of inflammatory reaction. Tissue death *en masse* appeared to be the outstanding feature of acute necrotic pancreatitis, and the transition from the altered to the normal parenchyma in the microscopic and macroscopic specimens was sharp. Hemorrhagic pancreatitis revealed the gland to be dark red and markedly engorged. Microscopically the extravasated blood and fibrin predominated, whereas the degeneration appeared to be secondary, followed by a minimal infiltration of polymorphonuclear cells. Most of the remaining cell nuclei showed pyknosis; others had completely disappeared.

In cases 14 and 35 the pathologic characteristics of acute edematous pancreatitis with fat necrosis were exhibited. The interstitial tissue of the gland was markedly edematous and infiltrated by a small number

of mononuclear and polymorphonuclear cells. Large accumulations of interacinar edema were observed. There was glossy edema of the surrounding viscera, and no evident pancreatic hemorrhage or necrosis could be demonstrated. The gland was considerably enlarged and distinctly firm to palpation. Twenty cases in the present series, or 57 per cent, revealed bile-stained or blood-stained free peritoneal fluid at operation.

CLINICAL MANIFESTATIONS

The value of hospital records in a collected series of cases such as this is only as reliable as the diligence and consideration given the anamnesis and physical examination. Too often the diagnosis of acute



Values for serum amylase in 4 cases of acute pancreatitis. Case 35, described in the text, was a case of type 1 acute edematous pancreatitis with fat necrosis. In cases *A* and *B* the pancreatitis was of types 3 and 4 respectively. More complete amylase studies in these cases were not available. In case *C* a carcinoma of the ampulla of Vater was resected. Autopsy performed on the eighth postoperative day revealed subsiding localized pancreatitis and areas of fat necrosis. Concomitant values for blood sugar were within normal limits in every instance.

pancreatitis is not made because it is not thought of. Such helpful questions as those concerning the exact character and localization of pain and its sharply defined point of radiation are not infrequently neglected, partiality being shown to the more commonplace symptoms of the "run-of-the-mill acute gallbladder." A statistical survey of the reported clinical records of other investigators reveals a familiar lack of uniformity, which, if it can be explained at all, is probably more apparent than real.

Age Incidence.—Acute pancreatitis may occur at almost any age, authentic cases having been reported in which the patients were aged 2 years and 77 years, respectively, but in the present group 60 per cent of the patients were between 30 and 50 years of age. There seemed to be no predilection of mortality for the aged or the young, but death was distributed uniformly through the middle-aged group.

Decade	Cases of Acute Pancreatitis
First	1
Second	0
Third	6
Fourth	9
Fifth	11
Sixth	6
Seventh	2

Sex Incidence.—Acute pancreatitis appears to be more common among women than among men, which is in accord with its relation to disease of the gallbladder and obesity. Fatalities occurred in direct proportion to the sexual incidence and seemed far more dependent on the pathologic type of the disease than on either the age or the sex of the patient.

	Males	Females
Schmieden and Sebening (1927)	520	980
McWhorter (1932)	32	32
Fallis and Plain (1939)	14	12
Peiser (1902)	79	42
Present series	8	27

Annual Incidence.—The yearly incidence of acute pancreatitis varied irregularly. A larger number of cases was observed during the last seven years than during the preceding twelve, but this was roughly proportional to the increased number of admissions to the hospital. There was no apparent seasonal preponderance, the cases being evenly distributed throughout the year.

Year	Cases	Year	Cases	Year	Cases
1921	4	1927	0	1933	5
1922	3	1928	1	1934	0
1923	0	1929	2	1935	3
1924	3	1930	0	1936	2
1925	1	1931	1	1937	3
1926	1	1932	1	1938	2
				First 5 months of 1939	2

Gastrointestinal History.—A past history of previous attacks was noted in 71 per cent of the present series. In most these attacks were similar in character and locale to the present illness but milder in severity. Indigestion and rather vague abdominal distress were recorded in 37 per cent of the cases. Complete freedom from any previous gastrointestinal complaints was found in only 17 per cent, whereas reference to the subject was omitted in 11 per cent of the anamneses.

Pain.—Despite its diverse etiologic and pathologic nature, acute pancreatitis constantly exhibits a sudden onset of rather severe pain. Except for several cases of type 1 pancreatitis, in which the pain was insidious and mild, this was uniformly so in every instance. Persistent epigastric pain was present in 57 per cent, pain in the upper part of the abdomen in 20 per cent, and pain in the right upper quadrant in 20 per cent of the cases. Pain in the left lower quadrant of the abdomen and precordial pain were each recorded on one occasion, although no apparent explanation for this localization was found at the time of operation.

Radiation of pain was noted as present in 74 per cent and absent in 9 per cent of the cases. The numerical incidence of the places to which the pain radiated occurred as follows: back, 21; right shoulder, 3; interscapular region, 3; left shoulder, 1, and umbilicus, 1. No indication of the exact point of radiation in the back was given.

Moynihan (1925) has given a picturesque clinical description of acute pancreatitis. He described the pain of this formidable catastrophe to be by far the worst of all the pains that the human body can suffer. This is undoubtedly true of the hemorrhagic and necrotic types of pancreatic lesions, but with the more benign acute edematous pancreatitis a gnawing, burning pain of lesser intensity is frequently to be encountered.

Vomiting was present in 71 per cent of the cases as recorded in the tabulation. Nausea appeared to be even more constant. The abdominal signs, although persistently found, seemed to be variable in locale and severity. There was no direct relation between the degree of tenderness and the type of pancreatic lesion. Tenderness occurred in the epigastrium in 14 cases, across the upper part of the abdomen in 11 cases and in the right upper abdominal quadrant in 7 cases. Rigidity was present at the time of the entrance examination in 60 per cent of the cases, and the point of maximum muscle spasm was usually the site of maximum tenderness. In general, rigidity was not marked. Jaundice was observed in 43 per cent of the cases. Explanations of its origin are speculative, and the prognostic value of its presence is most uncertain. The cyanosis described by Halsted (1901), a slate gray tinge most noticeable in the upper part of the body, was commented on in only 2 cases. Shock was noted in 3 instances. A definitely palpable mass was felt in 3 cases, although several additional records noted a "suggestive mass" observed by individual examiners. The temperature on admission is indicated in the tabulation of cases. The range of elevation of temperature appeared low and variable and unrelated to the prognosis. The pulse taken at the same time corresponded with the temperature and was in general surprisingly low. As was pointed out by Fallis and Plain (1939), this is at variance with the concept of shock, which

has been thought to be an outstanding symptom of acute pancreatic necrosis. The duration of the attack given in table 2 indicates the length of time from the initial onset of the present illness until the time of operation. In many cases the patient entered the hospital soon after onset of the attack but operation was deferred several days or longer.

TABLE 2.—*Summary of the Clinical and Laboratory Data in the Present Series of Cases*

	Duration of Attack	Vomiting	Jaundice	Tenderness	Rigidity	Temperature, F.	Pulse Rate	R.B.C., Millions per Cu. Mm.	W.B.C., per Cu. Mm.	Type of Pancreatitis	Resulting Condition of Patient
1	2 days	+	0	RUQ	UA	103.4	146	...	27,400	3	Improved
2	6 days	+	+	UA	UA	100.4	69	...	11,100	1	Well
3	6 days	+	+	RUQ	0	100.2	90	...	11,000	3	Well
4	4 days	+	0	UA	UA	101.4	134	...	.....	1	Well
5	3 days	+	0	UA	RUQ	99.2	84	4.8	12,400	1	Improved
6	3 days	+	0	UA	UA	98.2	100	4.4	13,800	2	Well
7	7 days	0	+	RUQ	0	98.4	92	3.8	21,500	1	Well
8	6 days	+	0	RUQ	RUQ	100.2	104	4.9	10,200	1	Well
9	2 days	+	+	Epig.	Epig.	100.0	74	3.75	11,800	1	Well
10	4 days	+	0	UA	0	101.2	100	4.28	10,800	2	Dead
11	3 days	+	0	Epig.	0	101.6	130	...	.....	1	Well
12	4 days	+	+	Epig.	0	101.2	116	...	.....	3	Dead
13	14 hours	..	..	UA	UA	99.4	82	...	.....	3	Dead
14	3 days	+	+	UA	UA	100.0	98	...	.....	1	Dead
15	10 hours	+	+	Epig.	Epig.	101.0	88	...	11,600	1	Well
16	2 days	+	0	Epig.	Epig.	100.6	96	...	13,100	1	Well
17	2 days	+	0	Epig.	..	100.6	112	3.7	14,000	1	Well
18	3 days	0	+	UA	RUQ	99.2	80	4.56	14,300	3	Improved
19	5 days	0	0	Epig.	..	103.0	116	4.5	22,000	3	Improved
20	10 days	+	0	RLQ	RLQ	102.4	100	4.4	11,000	1	Well
21	5 weeks	0	+	Epig.	..	99.4	84	...	.....	1	Well
22	5 days	+	+	LUQ	0	101.8	104	...	.....	3	Well
23	3 days	+	+	Epig.	..	101.6	112	...	.....	1	Well
24	7 days	..	..	RUQ	..	102.0	104	...	15,300	2	Improved
25	7 days	+	0	Epig.	Epig.	99.0	84	4.08	9,300	3	Improved
26	12 hours	+	..	UA	UA	99.8	72	6.0	28,500	2	Dead
27	8 days	0	0	Epig.	Epig.	100.8	84	4.19	11,900	1	Well
28	3 weeks	0	+	RUQ	RUQ	99.8	88	4.66	24,000	4	Well
29	7 days	+	0	UA	..	103.8	118	4.5	13,900	4	Improved
30	2 weeks	+	..	Epig.	Epig.	99.6	96	4.5	12,300	1	Well
31	6 days	+	+	RUQ	0	99.6	86	4.6	31,600	2	Dead
32	5 hours	+	0	UA	UA	101.4	100	5.01	21,400	3	Improved
33	2 days	..	..	Epig.	Epig.	.....	...	...	.....	1	Well
34	2 days	+	0	Epig.	0	101.0	100	...	16,000	1	Well
35	7 days	+	+	LUQ	Epig.	99.8	100	4.0	11,000	1	Well

The duration of attack (onset to operation) was difficult to determine accurately in cases in which repeated episodes had occurred during the present illness.

RUQ, right upper abdominal quadrant; LUQ, left upper abdominal quadrant; RLQ, right lower abdominal quadrant; UA, upper part of abdomen; Epig., epigastrium.

LABORATORY DATA

Hematologic Studies.—White blood cell counts revealed a wide range of individual variation, although 65 per cent of the reported counts were found to be below 15,000 per cubic millimeter. In cases in which differential counts were performed there was a marked predominance of polymorphonuclear cells. The red blood cell count offered but scanty new or diagnostically significant information regarding the patient's status. Mild anemia of the normocytic class was present in most cases,

and this was in no way severe, even in the presence of the acute hemorrhagic type of pancreatitis with considerable sanguinous peritoneal exudate.

Urinalysis.—Examination of the urine showed albuminuria in a large proportion of the cases. Glycosuria was relatively uncommon. Casts and leukocytes were found occasionally but had little significance.

Chemical studies of the blood were carried out sporadically, and consequently were of little value. Determinations of the amylase content of the blood, urine and feces were deficient in all cases except case 35, as the earlier methods and technic used were chemically questionable, and the results, expressed in unfamiliar units, were rather confusing.

DIAGNOSIS

The diagnostic indications of acute pancreatitis fall into three main groups. In the first are the clinical signs and symptoms; in the second are changes in the external pancreatic secretion, and in the third are changes in the internal pancreatic secretion. Results of roentgen examination in the diagnosis of pancreatic disease have thus far been barren. A survey of the literature clearly indicates that the diagnosis of acute pancreatitis is correctly made more often at operation or at necropsy than at the bedside. As has been mentioned, the diagnosis of acute pancreatitis was correctly made in only 11 per cent of the cases of this series. It was suggested as an alternative diagnosis in an additional 17 per cent. The preoperative impression in 70 per cent of the cases was that of acute disease of the gallbladder. Perforated peptic ulcer and acute appendicitis were considered as alternative diagnoses in 14 per cent and 10 per cent respectively.

Many ingenious tests of pancreatic function have been devised, each having its adherents and each its critics who question its utility. The eponymic tests of Cammidge and Loewi have been called esoteric by Coope (1927), who designated them as reactions of dubious foundation. Attempts to determine pancreatic function by examination of the feces and duodenal contents for enzymes have met with little success as practical diagnostic aids in cases of acute pancreatic disease. However, since Magendie (1846) first demonstrated the presence of amylase in blood serum there have been a considerable number of experimental and clinical data to recommend this test as a useful diagnostic adjuvant in cases of this condition. The work of Elman (1931 and 1937) and many others in America and abroad has shown a close correlation between the level of serum amylase and the coincident acute pathologic process in the pancreas. The conflicting results obtained by earlier investigators were probably due to a difference in the methods of amylase determination and must not impugn the reliability of recent, more

uniform reports. Somogyi (1938) has pointed out the inherent vulnerability of older methods, and he has suggested a standard set of conditions and a rapid and practical procedure which, in principle, is entirely in accord with the kinetics of enzyme chemistry.

Several hundred routine serum amylase determinations with a modified Somogyi technic but similar standards have given convincing evidence that the normal level of amylase remains within constant limits in practically all types of disease except acute pancreatitis, in which there is a sudden and significant marked rise. It has been my experience that thyroid and hepatic disease and diabetes may slightly lower the level of serum amylase and that decreased function of the kidney may cause failure of normal excretion of amylase, resulting in slight elevation of the value, but in no condition in which the clinical picture of an "acute abdomen" (other than acute pancreatitis) was present was the level of serum amylase so strikingly elevated. It is true, however, that this value usually reaches its peak within the first forty-eight hours of the disease, and it may precipitously return to normal again within the next forty-eight hours, thus limiting the reliability of the test to the early stages of the attack. Most clinical reports of serum amylase studies agree that in all types of acute pancreatitis there is a significant early rise, regardless of the severity of the lesion. My series of simultaneous determinations of urinary amylase frequently showed a higher value fluctuating within a wider range of individual variation, but generally corroborated the serum amylase level. As yet I have had only a limited experience with the diagnostic value of the serum lipase test, but the enthusiastic reports of Comfort (1937) and of Cherry and Crandall (1932) are an incentive to investigate more extensively and to further its clinical application. Regardless of technical differences both the serum lipase and the serum amylase tests offer valuable information in the diagnostic difficulty of acute pancreatitis, and, when properly evaluated with the clinical signs and symptoms, may reap the benefit of greater diagnostic accuracy and recognition. The fact that practically all observers who have had experience with the serum amylase test find it of genuine value indicates that its usefulness could be expanded, particularly if a conservative therapeutic attitude is to be taken. Peritoneal tap was not performed in this series of cases, but it is recommended by some clinicians as a desirable part of the diagnostic armamentarium.

TREATMENT

It was adequately demonstrated by Whipple and Goodpasture (1913) and by Cooke and Whipple (1918) that extensive surgical procedures on animals with experimentally produced acute pancreatic necrosis are contraindicated. The products of pancreatic destruction and peritoneal

exudate are essentially innocuous, and attempts at surgical detergence were of no distinct benefit to the animals. It was concluded from this that the power of pancreatic recuperation is greatest when the gland is left undisturbed in a closed abdomen. The general reaction and toxemia which may occur result from primary nonspecific cellular destruction of the pancreas and cannot be alleviated by operation.

Despite fifty years of surgical therapy, the high mortality of acute pancreatic necrosis remains disconcertingly unaltered. The operations resorted to have shown great diversity. Some surgeons favor immediate laparotomy, while others elect to defer operation. There is apparently no optimum interval for pancreatic appeasement, and thus operation is performed mainly in keeping with the custom of the individual surgeon. If the patient's condition justifies operation, there is considerable variation in the method or combination of methods. The pancreas is drained most commonly by splitting the overlying peritoneum or by dissecting the parenchyma of the gland and removing the necrotic tissue. Anatomically it is hoped that by incising the peritoneal covering of the pancreas its secretory tension will be relieved. However, each individual pancreatic lobule is enclosed by a separate capsule of connective tissue, and in order to insure relief of tension it would be necessary to divide the sheath of each lobule separately. The extensive nature of such a procedure is likely to cause more harm than good. Biliary decompression is accomplished by any one of several operations involving the gallbladder and common duct. The general lack of uniformity in the types of surgical procedures performed has been pointed out by Cole (1938), who suggested that "the value of operation might be overemphasized, although it is undoubtedly true that different procedures would be indicated in different cases."

Until recently there was unanimity of opinion advocating the surgical therapy of acute pancreatitis. Within the last few years, however, the critical reviews of several investigators have repudiated this concurrent belief and favored conservative treatment followed by interval operation if necessary. Nordmann (1938), a surgeon who has devoted a lifelong interest to the study of acute pancreatitis, found, in a careful and objective analysis of the subject, that when the diagnosis of acute pancreatitis can be safely made the omission of any surgical procedure is mandatory. His own case mortality fell from above 50 per cent to 24 per cent under a conservative regimen. Those of his colleagues who resorted to this surgical nihilism found a similar response. Walzel, Bernhard and Haberer found their respective mortality statistics more than halved by following this conservative course of therapy. Mikkelsen (1934) has fostered a Danish school of thought favoring expectant treatment in the care of this disease. He reported a 7.5 per cent mortality in a

personal series of 39 cases in which the patients were treated non-surgically, followed in several weeks by interval operation when indicated. Fifty per cent of his patients were acutely ill at the time of admission to the hospital. After immediate operation his mortality statistics were considerably higher. Walzel (1934) performed surgical exploration in 30 "emergency cases" between 1926 and 1928, with a resultant mortality of 87 per cent. Between 1928 and 1934 he treated 46 patients conservatively, performing an interval operation only when this was indicated by associated disease of the biliary tract, or a deferred operation for well localized suppurative pancreatitis, with a resultant low mortality of 28 per cent.

It is apparent from the literature that there is no agreement as to the comparative value of operative versus the conservative treatment of acute pancreatitis. Because of the infrequent occurrence of this disease the individual surgeon has little opportunity to draw conclusions from his own personal therapeutic experience; he must rely on the empiric dicta of distinguished surgeons who have decidedly influenced the vacillating regimen of treatment. Such prominent authorities as McWhorter (1932), Finney (1933), Körte (1912), Abell (1938), Eliason and North (1930), Wolfer (1926) and others have advocated early operation, whereas others equally authoritative—Lewis (1936), Wangensteen (1932), Nordmann (1938) and Walzel (1934)—have recommended conservative treatment or interval operation.

In the present series 4 patients were treated as "surgical emergencies" during the first twenty-four hours of the disease, with a 50 per cent mortality. The 2 patients who died had acute pancreatitis of types 2 and 3; the 2 who recovered had types 1 and 3. Thirty-one patients were operated on during the first week of illness, with a 20 per cent mortality. Of the latter group almost 50 per cent had type 1 —acute edematous pancreatitis. The 4 patients treated surgically after the first week of the disease fared still better; all recovered. The average mortality for all types of the disease was 17 per cent, which is rather a decided diminution from the reported operative death rate of other investigators. A more careful study of the deaths from the different types of pancreatitis (table 3) indicates that the mortality rate is directly dependent on the pathologic involvement of the gland and the type of acute pancreatitis. The fact that 54 per cent of the patients in the present series had the mild and less severe phase of the disease is at least a likely explanation of this estimable low mortality figure. The short span of postoperative life has been commented on by many other investigators, and the question has been raised as to the patient's ability to withstand immediate operation. Death within the first two postoperative days was noted in 66 per cent of the fatalities in this

series. Failure to rally or respond to postoperative therapy was mentioned in the case histories and would appear to corroborate the belief that the added insult of emergency operation was more than the patient's condition warranted.

Table 5 indicates the operative procedures followed in the present series of cases. Incision and drainage of the pancreas in combination

TABLE 3.—*Incidence and Mortality Rate of the Four Types of Acute Pancreatitis*

	Type 1 (Acute Edematous Pancreatitis)		Type 2 (Acute Hemorrhagic Pancreatitis)		Type 3 (Acute Necrotic Pancreatitis)		Type 4 (Acute Suppurative Pancreatitis)	
	Incidence, per Cent	Mortality, per Cent	Incidence, per Cent	Mortality, per Cent	Incidence, per Cent	Mortality, per Cent	Incidence, per Cent	Mortality, per Cent
McWhorter (1932), 64 cases	28	28	42	70	11	70	19	50
Schmieden and Sebening (1927), 1,278 cases*	45	34	25	64	22	66	8	60
Abell (1938), 30 cases	30	0	33	50	30	44	7	0
Present series (1939), 35 cases	54	5	14	60	26	22	6	0

* The cases of Schmieden and Sebening have been grouped into this pathologic classification.

TABLE 4.—*Statistics on the Reported Personal Series of Cases of Acute Pancreatitis*

Observer	Number of Cases	Mortality, per Cent	Comment
1. Quick (1932)	21	38	Early operation; cholecystectomy and choledochostomy were the procedures of choice
2. Abell (1938)	30	30	Early operation favored; cholecystostomy and peritoneal drainage (Penrose) were the procedures of choice
3. Walzel (1926-1928)	30	87	Early operation in all cases
4. Walzel (1928-1934)	46	28	Conservative treatment or delayed operation
5. Schmieden and Sebening (1927)	38	..	Cholecystectomy and choledochostomy were the procedures of choice
6. Mikkelson (1934)	39	7.5	Conservative treatment; delayed operation only when indicated
7. Present series (H. E. Isaacs)	20	15	Cholecystectomy and incision and drainage of the pancreas were the procedures of choice

with one or more ancillary measures were performed in 77 per cent of the cases. In the remaining 23 per cent, in which the pancreas was not disturbed, there were no deaths. Despite the obvious variety of operative procedures followed in this series of cases, as well as in the personal cases previously reported by individual surgeons (table 4), the diverse mortality statistics signify that an ideal type of therapy for

this disease is yet to be found. Regardless of the operation, the operator or the lack of operation, the mortality of this condition appears to be primarily a result of the pathologic process in the pancreas, and future therapy will undoubtedly be governed by the progress made toward better understanding and control of the origin of pancreatic necrosis. Fact, established by careful correlation of experimental and clinical data, must replace theory and habit before adequate prophylaxis and treatment prevail. Improved diagnostic aids now favor a concerted effort toward more effective therapy, whether it be conservative measures, modified surgical measures or chemotherapy. The virtue of sulfanilamide or its derivatives as an aid in the treatment of acute pancreatitis is as yet undemonstrated.

TABLE 5.—*Operative Procedures Employed in the Present Series of Cases*

Operation	Number of Cases	Mortality, per Cent
1. Cholecystostomy and incision and drainage of the pancreas	5	40
2. Incision and drainage of the pancreas	4	25
3. Cholecystectomy and incision and drainage of the pancreas	12	25
4. Cholecystectomy, appendectomy and incision and drainage of the pancreas	2	50
5. Cholecystectomy	3	0
6. Cholecystectomy and choledochostomy	3	0
7. Cholecystectomy, choledochostomy and incision and drainage of the pancreas	3	0
8. Cholecystostomy, appendectomy and incision and drainage of the pancreas	1	0
9. Cholecystostomy	1	0
10. Laparotomy	1	0

SUMMARY AND CONCLUSIONS

Acute pancreatitis is a dangerous disease the rarity of which has been overestimated. Important laboratory diagnostic aids, namely, studies of the serum amylase and lipase, indicate that acute pancreatitis may be milder and more prevalent than has been thought.

A consideration of the factors of pathogenesis demonstrates a significant relation of acute pancreatic necrosis to organic diseases and to functional disturbances of the biliary tract. Etiologic agents which seem incapable of producing this disease when acting individually may play a principal pathogenic role when combined. Four separate pathologic types of pancreatitis have been distinguished, and each must be afforded individual attention regarding diagnosis, prognosis, prophylaxis and treatment.

Thirty-five operative cases of acute pancreatitis are reported, with a mortality of 17 per cent. Of these, 54 per cent were of type 1—acute edematous pancreatitis, a rather benign phase of the disease. Pain and tenderness, most often in the epigastrium or the upper part of the abdomen, were constant clinical findings. Radiation of pain to the back,

vomiting and a past history of recurrent attacks similar to the present illness were noted frequently.

Incision and drainage of the pancreas combined with one or more ancillary procedures were performed in 77 per cent of the cases in the present series. Beneficent experience in using the serum amylase test as a helpful aid in diagnosis may tend to modify conservatively the future surgical treatment of acute pancreatitis.

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LYMPH IN EXPERIMENTAL BURNS

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Many studies have been made on the subject of toxin formation as a result of burns. The fact that such abundant evidence both for and against the formation and absorption of toxin has been collected attests to the difficulty of experimentally proving or disproving its existence.

Most of the recent studies have been directed either toward demonstration of a toxin in the blood of burned animals or toward its demonstration in extract from the burned area itself. Thus Robertson and Boyd [1] reported that they had found a toxin in the whole blood and in the cells of burned animals which was not present in the serum and that alcoholic extracts of burned skin proved toxic on injection into guinea pigs, whereas similar extracts of normal skin produced no toxic symptoms. Their second study was repeated by Underhill and Kapsinow,[2] who found that an alcoholic extract of normal skin was just as toxic as a similar extract of burned skin and concluded that the lethal factor in both cases was the alcohol. Harrison and Blalock noted,[3] contrary to the findings of Robertson and Boyd, that isotransplantation of burned skin had no effect on the recipient animal; that transfusion of blood from burned to normal dogs produced no toxic symptoms, and that débridement of the burned area shortened the survival of burned animals.

Harkins, Wilson and Stewart,[4] working with a protein-free extract of skin, demonstrated a depressor substance in both normal and burned rabbit skin. The depressor activity of the extract of burned skin was often less than that of the extract of normal skin. Wilson, Jeffrey,

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Aided by a grant from the Division of Medical Science of the Rockefeller Foundation.

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Roxburgh and Stewart [5] reported that the edema fluid collected from burned areas in rabbits gradually acquired toxic properties and when collected forty-eight hours after burning was frequently lethal to healthy animals of the same species. This action was independent of bacterial activity and seemed to be dependent on the autolysis of injured tissue.

In 1937, Rosenthal [6] reported the finding of a substance in the blood of burned shoats, pigs, guinea pigs and human beings which caused contraction of the virgin guinea pig uterus. It was at first linked with the red blood cells but was later found in the serum, and its properties were sufficiently distinct from those of histamine to differentiate it from that substance. The serums of convalescent burned animals were found to have the power of neutralizing the substance, but normal serum also had this action to a less marked extent. Kinard and Martin,[7] in studying the vasodepressor action of assay solutions prepared from the blood of normal and that of burned dogs by the Best and McHenry method, concluded that the vasodepressor activity is not due to histamine and that the increased vasodepression produced by assay solutions of blood from burned dogs is accounted for by the increased blood protein concentration due to loss of fluid. They expressed the opinion that the vasodepressor action of the solutions may be due to a protein split product formed from the blood protein during preparation of the assay solution.

The subject of the absorption of substances from burned areas is also somewhat controversial. Thus Underhill, Kapsinow and Fisk [8] reported that after a short latent period the absorption of phenolsulfonphthalein and strychnine from burned areas was much slower than under normal conditions and that substances such as trypan blue, when injected intravenously, readily passed from the blood stream into the burned area but were not reabsorbed to any significant extent. They suggested that the fluid shift in burns resulting from increased capillary permeability is in one direction only, from the capillaries to the tissues. Mason, Paxton and Shoemaker [9] used this same experimental technic

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9. Mason, E. C.; Paxton, P., and Shoemaker, H. H.: A Comparison of the Rate of Absorption from Normal and Burned Tissues, Ann. Int. Med. **9**:850-853, 1936.

with sodium iodide and reported that excretion of this substance in the urine was almost identical in the control and in the burned animals.

Moon,[10] in discussing traumatic toxemia as a cause of shock, stated:

> Efforts have been made by the transfusion of blood and otherwise to demonstrate poisonous substances in the blood of animals in shock. The uniformly negative results of such experiments have been emphasized by some as invalidating the conception of traumatic toxemia. Surgeons have made this objection more vigorously than physiologists, perhaps because the latter remember that protein and colloidal substances are not absorbed from tissue spaces into the blood stream but via the lymphatics.

Field and Drinker[11] found that the capillaries are not concerned with absorption of protein from the subcutaneous tissues under normal circumstances but that after plasmapheresis, with substantial reduction of total blood protein, foreign protein placed in the subcutaneous tissues can be detected serologically in the blood when entrance by lymphatic routes has been blocked.

The present study consists primarily of a biologic assay for depressor substances in unmodified lymph obtained from the thoracic duct at varying intervals after receipt of a burn. In several instances, also, dyes were injected into the burned areas, and the lymph of the thoracic duct was observed for evidence of lymphatic absorption of the dye.

METHOD

Large animals were anesthetized with ether, and burns were produced by application of red hot soldering irons to the posterior extremities and the lower part of the abdomen. Each hind quarter was burned for approximately five minutes, the resultant burned area comprising approximately one fifth to one seventh of the whole surface. This had been found to be approximately the maximal thermal injury consistent with survival through the period of experimentation. After this procedure the animals were allowed to live normally until ten or twelve hours prior to the lymph studies, when all food and water were withdrawn, to minimize the amount of lymph entering the thoracic duct from the gastrointestinal tract. The animals were then anesthetized with intraperitoneal pentobarbital sodium (25 to 30 mg. per kilogram of body weight) and the thoracic duct was cannulated, the external jugular vein being utilized as a conduit. All visible tributary veins and lymphatics from the neck, upper extremities and wall of the chest were ligated. The collection of lymph was facilitated by moderate negative pressure, usually 20 to 30 cm. of water. Anesthesia was maintained by intraperitoneal pentobarbital sodium during the period of collection of lymph, and the animals were killed at the end of this period. In several instances Evans' blue azo dye (5 cc. per extremity) was injected

10. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938, p. 151.

11. Field, M. E., and Drinker, C. K.: Conditions Governing the Removal of Protein Deposited in the Subcutaneous Tissues of the Dog, Am. J. Physiol. **98**: 66-69, 1931.

without pressure beneath the eschar on the medial and lateral aspect of the thigh two to three hours before termination of the experiment, and the lymph was carefully observed for evidence of its absorption.

The unmodified lymph was tested for vasodepressor activity by the method described by Grossman and Williams.[12] This consists of cannulating the abdominal aorta of an albino rat anesthetized with pentobarbital sodium (4 to 5 mg. per hundred grams of body weight) and connecting this cannula by means of a three-way stopcock to a small bore mercury manometer for direct reading of the aortic blood pressure or to a syringe for injection of lymph. A small quantity of heparin was introduced as an anticoagulant, and control pressures were obtained. The amount of lymph injected was arbitrarily set at 0.5 cc. per hundred grams of body weight, and this was injected over a period of forty-five seconds. Blood pressure readings were obtained at fifteen second intervals for approximately three minutes,

Studies of Lymph in Experimental Burns

Experiment	Interval Between Receipt of Burn and Beginning of Lymph Collection		Period of Lymph Collection		Amount of Lymph Collected, Cc.	Approximate Change* in B. P. Induced in Rat by Dose of 0.5 Cc./100 Gm.	Appearance of Dye in Lymph
	Hr.	Min.	Hr.	Min.			
1	..	..	5	15	44	0	Not injected
2	2	10	1	20	18	0	Not injected
3	12	..	7	50	45	0	Did not appear
4	17	40	6	50	158	0	Did not appear
5	24	..	11	30	109	0	Not injected
6	42	30	6	..	91	0	Not injected
7	47	20	7	..	122	0	Did not appear
8	69	45	7	..	13	0	Did not appear
9	96	45	2	..	21	0	? Faint trace after 45 min.
10	90	30	2	30	7.5	0	? Faint trace after 2 hr.
11	71	15	1	..	104	0	? Faint trace after 30 min.
12	71	10	2	..	80	0	Did not appear
13	114	..	7	..	36	0	Did not appear
14	141	..	7	..	8	0	Did not appear
15	165	..	8	..	5	0	Did not appear

* Change in blood pressure is recorded as zero if it did not exceed ± 8 mm. of mercury.

at thirty second intervals for approximately six minutes and at one minute intervals for approximately fifteen minutes.

Similar studies were made on 3 normal animals to serve as controls.

RESULTS

No vasodepressor activity could be demonstrated in the lymph from normal animals. A total of 15 experiments were performed on burned animals at intervals up to one hundred and sixty-five hours from the time of receipt of the burn. In none of these experiments could a vasodepressor substance be demonstrated in the lymph of the thoracic duct when this substance was tested by intra-arterial injection into the albino rat. In a few instances there was a slight transient rise in the arterial

12. Grossman, E. B., and Williams, J. R., Jr.: Relation of Age to Renal Pressor Substance, Arch. Int. Med. **62**:799-804 (Nov.) 1938.

pressures following the injection, but this never exceeded 8 mm. of mercury and so was interpreted as a volume effect.

The natural opalescent character of lymph made positive identification of minute quantities of the blue dye difficult and the results not conclusive. One would, however, get the impression that Evans' blue dye is poorly absorbed by the lymphatics draining burned areas.

In several instances in which the regional nodes were examined no dye could be demonstrated, and the distribution of the dye appeared to be limited to the areas into which it had been injected.

The results of these experiments are presented in the accompanying table.

COMMENT

The fact that no vasodepressor substances could de demonstrated in lymph from the thoracic duct of burned animals may have three possible explanations: (1) There may be no such substance formed; (2) if such a substance is formed, its lymphatic absorption may be negligible, and (3) because of lymphodilution, the method of assay used in these experiments may not have been sensitive enough to detect minute quantities which may have been present.

This study can offer no evidence either for or against the existence of a toxin in the burned area itself, but demonstration of such a poison is of minor significance when compared to the question of its absorption. In order to exert a detrimental effect on the organism as a whole, the hypothetic toxin must be absorbed either directly into the blood stream or indirectly via the lymphatics. In regard to the latter, there is some evidence (i. e., the absence of any significant lymphatic absorption of dyes) that suggests that lymphatic absorption from burned areas may be considerably impaired. Thus it is possible that the lymph of the thoracic duct, which was tested for depressor substances, contained little or no lymph from the burned area. If this be true, one could hardly expect to demonstrate in it a toxin which could not be absorbed because of impaired lymphatic function.

In any study on lymph collected from the larger lymph vessels there is the constant and unavoidable factor of dilution of lymph. Because of this, any toxin which might be present could conceivably be so dilute that its presence could not be demonstrated by standard assay methods. In the present study this factor was minimized by injecting relatively large quantities of lymph into small animals.

SUMMARY

Lymph collected from the thoracic ducts of burned animals has been tested for vasodepressor activity by intra-arterial injection into albino rats. No vasodepressor activity was demonstrated by this method of study.